FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Meeting of the

Anesthetic and Life Support Drugs Advisory Committee

(ALSDAC)

and the

Drug Safety and Risk Management Advisory Committee

(DSaRM)

OPEN SESSION

THURSDAY, SEPTEMBER 24, 2009

9:15 a.m. to 4:15 a.m.

Holiday Inn Gaithersburg

Two Montgomery Village Avenue

Gaithersburg, Maryland

Anesthetic and Life Support Drugs Advisory Committee

Members *(Voting)*

Jeffrey R. Kirsch, M.D. ***(Acting Chair)***

Professor and Chair

Department of Anesthesiology & Peri-Operative

Medicine

Oregon Health & Science University

Portland, Oregon

Jayant K. Deshpande, M.D.

Department of Anesthesiology

Division of Pediatric Anesthesiology

Monroe Carrell Jr. Children’s Hospital at Vanderbilt

Nashville, Tennessee

Donald S. Prough, M.D.

Professor and Chairman

Department of Anesthesiology

The University of Texas

Medical Branch at Galveston

Galveston, Texas

Daniel Zelterman, Ph.D.
Professor and Acting Division Head
Division of Biostatistics, Epidemiology & Public Health
Yale University School of Medicine
New Haven, Connecticut

Anesthetic and Life Support Drugs Advisory Committee Member *(Non-voting)*
Bartholomew J. Tortella, M.T.S., M.D.
Industry Representative
Senior Director, Trauma and Critical Care Research
Novo Nordisk, Inc.
Princeton, New Jersey

Drug Safety and Risk Management Advisory Committee Members *(Voting)*
Timothy S. Lesar, Pharm.D.
Director of Pharmacy
Albany Medical Center
Albany, New York

Allen J. Vaida, Pharm.D., FASHP
Executive Vice President
Institute for Safe Medication Practices
Horsham, Pennsylvania

Temporary Voting Members

William Cooper, M.D.
Professor of Pediatrics and Preventive Medicine
Vanderbilt University
Nashville, Tennessee

Stephanie Crawford, Ph.D.
University of Illinois at Chicago
Chicago, Illinois

Richard A. Denisco, M.D., M.P.H
Medical Officer
Division of Epidemiology, Services and Prevention Research
National Institute on Drug Abuse
Bethesda, Maryland

Ruth S. Day, Ph.D.
Director, Medical Cognition Laboratory
Duke University
Durham, North Carolina

Jacqueline Gardner, Ph.D.
University of Washington
Health Science Building
Seattle, Washington

Randall Flick, M.D.
Assistant Professor of Anesthesiology
Mayo Clinic
Department of Anesthesiology
Rochester, Minnesota

Karl Lorenz, M.D., M.S., H.S.
Assistant Professor of Medicine
Geffen School of Medicine at UCLA
Veterans Affairs
Greater Los Angeles Healthcare System

Los Angeles, California

David Margolis, M.D., Ph.D. *(by telephone)*

Professor of Dermatology

Professor of Epidemiology

University of Pennsylvania

Philadelphia, Pennsylvania

John Markman, M.D.

Director, Translational Pain Research

Director, Neuromedicine Pain Management

University of Rochester Medical Center

Rochester, New York

Elaine Morrato, Dr.P.H., M.P.H., C.P.H.

Assistant Professor

University of Colorado Denver

Denver, Colorado

Deborah Shatin, Ph.D.

Principal

Shatin Associates, LLC

Plymouth, Minnesota

Martha Solonche
(Patient Representative)
New York, New York

Michael L. Yesenko, M.D.
(Patient Representative)
Lead Public Health Advisor
Department of Health and Human Services
Substance Abuse and Mental Health Services
Administration (SAMHSA)
Rockville, Maryland

Julie Zito, Ph.D.
Professor
Pharmaceutical Health Science Research
University of Maryland
Baltimore, Maryland

1

FDA Center for Drug Evaluation and Research

Participants at the Table *(Non-voting)*

John K. Jenkins, M.D.
Director, Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

Sharon Hertz, M.D.
Deputy Director
DAARP, CDER, FDA

Ellen Fields, M.D., M.P.H.
Clinical Team Leader
DAARP, CDER, FDA

Robert Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and
Rheumatology Products (DAARP)
CDER, FDA

Henry Francis, M.D.

Deputy Director, Office of Surveillance and Epidemiology (OSE)

CDER, FDA

I N D E X

AGENDA ITEM

PAGE

Adjourn

293

P R O C E E D I N G S

9:15 a.m.

DR. KIRSCH: Good morning. My name is Jeffrey Kirsch. I'm the chair of this committee, and I serve as Chair of the Department of Anesthesiology in Portland, Oregon.

Good morning, everybody. I would first like to remind everyone present to please silence your cell phones, if you've not already done so. I'd also like to identify the FDA press contact who's Karen Mahoney -- and if she's here; there she is in the back -- for the press if you have any questions.

I'd like to first read a statement, the following. For topics, such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if

they're recognized by myself, the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during the breaks or lunch. Thank you.

I next would like to have the members of the committee introduce themselves and we'll start with the FDA.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs at FDA.

DR. RAPPAPORT: I'm Bob Rappaport. I'm the

Director of the Division of Anesthesia, Analgesia, and Rheumatology Products.

DR. HERTZ: Sharon Hertz, Deputy Director, Division of Anesthesia, Analgesia, and Rheumatology Products.

DR. FIELDS: Ellen Fields, Clinical Team Leader, Division of Anesthesia, Analgesia, and Rheumatology Products.

DR. FRANCIS: Good morning. Henry Francis, Deputy Director, the Office of Surveillance and Epidemiology.

DR. PROUGH: Don Prough, Chairman, Anesthesiology, at the University of Texas in Galveston.

DR. ZITO: Julie Zito, University of Maryland, Baltimore, pharmacoepidemiologist.

DR. COOPER: Bill Cooper. I'm a general pediatrician and a pharmacoepidemiologist at Vanderbilt University in Nashville, Tennessee.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois at Chicago, College of Pharmacy.

DR. DESHPANDE: Jayant Deshpande, Pediatric Anesthesia and Critical Care, from Vanderbilt University in Nashville.

DR. MARKMAN: John Markman, Neurology and Pain Management, University of Rochester School of Medicine, Rochester, New York.

DR. DAY: Ruth Day, Director of The Medical Cognition Laboratory at Duke University.

DR. LORENZ: Karl Lorenz. I'm a palliative medicine physician and a primary care internal medicine physician with The Veterans Administration, UCLA, and RAND Health.

MS. BHATT: Kalyani Bhatt. I'm the Designated Federal Official, FDA.

DR. ZELTERMAN: Dan Zelterman. I'm in the Division of Biostatistics at Yale University.

DR. SOLONCHE: Martha Solonche, Patient Representative, from New York City.

DR. DENISCO: Richard Denisco, Medical Officer, National Institutes of Health.

DR. MORRATO: Elaine Morrato, epidemiologist, from the Colorado School of Public

Health, University of Colorado, Denver.

DR. LESAR: Timothy Lesar, Director of Clinical Pharmacy Services, Albany Medical Center, in Albany, New York.

DR. SHATIN: Deborah Shatin, pharmacoepidemiologist, Shatin Associates, LLC, Minnesota.

DR. VAIDA: Allen Vaida, Executive Vice President, at the Institute for Safe Medication Practices. I'm a pharmacist.

MR. YESENKO: Michael Yesenko, Patient Representative, Brookeville, Maryland.

DR. FLICK: Randall Flick, Chief of Pediatric Anesthesia, Mayo Clinic.

DR. TORTELLA: Bartholomew Tortella, Novo Nordisk, Industry Representative.

DR. KIRSCH: Thank you. I'd like now to have Kalyani Bhatt read the Conflict of Interest Statement.

MS. BHATT: Good morning. Thank you. Before I start, we also have Dr. David Margolis by teleconference.

DR. MARGOLIS: Hi. I'm David Margolis. I'm at the University of Pennsylvania. I'm in the Department of Dermatology and Department of Biostatistics and Epidemiology. I'm quarantined in my office because my youngest son had H1N1 a couple days ago.

MS. BHATT: Thank you, Dr. Margolis.

The Food and Drug Administration, FDA, is convening today's Joint Meeting of the Anesthetic and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the Industry Representative, all members and temporary voting members of the committees are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC Section 208 and Section 712

of the Federal Food, Drug, and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws under the 18 USC Section 208.

Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well

of their imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, gratis, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussion of New Drug Application NDA-22-272 OxyContin, OxyContin Hydrochloride Controlled-release Tablets, sponsored by Purdue Pharma LP, and its safety for the proposed indication of management, moderate to severe, when continuous around-the-clock analgesic is needed for extended period of time.

This formulation was previously reviewed and discussed by these committees on May 5th, 2008, and will be considered again in light of new data. This topic is a particular matter involving specific parties.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of

interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we'd like to disclose that Dr. Bartholomew Tortella is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry.

Dr. Tortella's role at this meeting is to represent industry in general and not any particular company. Dr. Tortella is employed by Nova Nordisk, Incorporated.

We'd like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has personal or imputed financial interests, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, including consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest in those based upon the outcome of the meeting.

Thank you.

DR. KIRSCH: Thank you. I'd like to ask Ellen Fields from FDA to start our session.

DR. FIELDS: Good morning. Dr. Kirsch, members of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees, invited guests, thank you for joining us today. To those of you who were not here yesterday, welcome, and to those of you who were here yesterday, we appreciate your returning for a second day of discussion regarding another potent modified release opioid product.

As I said in yesterday's opening remarks, we are faced with balancing the risks and benefits of new formulations of opioid drug products related to

two important public health concerns: the increase in the misuse, abuse, and diversion of these products and the unmet needs of pain patients living with inadequately-treated pain.

We heard yesterday, and we'll hear again today, a great deal of information concerning the abuse and diversion of prescription opioid drug products in the United States. Clearly, as a public health agency, we must find better ways to address this public health crisis.

At the same time, we are also responsible for maintaining access to these critically-important drug products for legitimate patients.

During the open public session yesterday, we heard the personal stories of patients with inadequately-treated chronic pain and the enormous impact this has on the quality of their lives and the lives of their families.

Today, we will be discussing Purdue's reformulation of OxyContin, designed to resist attempts to defeat the physical-chemical properties that make it an extended-release formulation. The

same product was presented at the Joint Advisory Committee meeting on May 5th, 2008, which many of you attended and at which time the risks and benefits of this new formulation were discussed.

The members of the committees were asked to decide whether there was sufficient evidence to support whether the controlled-release mechanism of the new OxyContin formulation was less likely to be defeated than the earlier formulation and how this might impact the abusability of the product.

The members were also asked to discuss what would constitute an adequate degree of abuse resistance to warrant changes to a product’s label.

The overall consensus of the members at the May 5th meeting was that the available data were not adequate to evaluate whether the new OxyContin formulation would be less likely to reduce its abuse, misuse, or diversion.

Purdue’s intention at the time of the May 5th meeting was to market the reformulated OxyContin only in the 10, 20, 30, and 40 milligram strengths and to maintain the non-reformulated 60 and 80

milligram strengths on the market at the same time, reformulating these higher-strength doses in the future.

The committee members recommended that the higher non-reformulated strengths of OxyContin should not remain on the market if the lower reformulated strengths were to be approved due to the possibility that prescribers would assume the higher-strength formulations were also an abuse-deterrent, potentially resulting in a number of safety concerns.

The committee's opinion on whether the label should include any language regarding the tamper-resistant properties of the product was mixed. The reformulated OxyContin was not approved at that time because the studies of the effects of the physical and chemical manipulation of the new formulation were not conducted with adequate rigor and did not result in information that would allow determination of the actual degree of tamper resistance that exists for the formulation.

Purdue has resubmitted the NDA for the reformulated OxyContin with additional data regarding

the physical-chemical attributes of the product. They are proposing to market only the reformulated OxyContin as all strengths have now been reformulated and to remove the currently-approved formulation from the market.

In contrast to the application reviewed at the advisory committee on May 5th, in the current application, Purdue has not requested labeling to support abuse-resistant claims.

Following presentations from Purdue and FDA, you will be asked to discuss whether the studies performed by the sponsor are adequate to provide data on the abuse-deterrent characteristics of the reformulated OxyContin product, whether the change in formulation affects the overall safety profile of OxyContin, and whether this application for reformulated OxyContin should be approved.

We hope with your varied expertise and extensive experience will help us answer these important questions. Thank you for assisting us with this challenging task.

DR. KIRSCH: Next on the agenda is

Anjelina, I can't pronounce the last name. Anjelina P. Dr. Anjelina.

DR. POKROVNICHKA: Good morning. That's actually how patients refer to me, as well.

My name is Anjelina Pokorvnichka, and I'm a medical reviewer in the Division of Anesthesia, Analgesia, and Rheumatology Products.

My presentation will outline the history of OxyContin to date and will include important changes to the product label and a discussion of the risk management activities for OxyContin.

OxyContin was approved in December of 1995. The approval occurred during a period of growing recognition that many patients with chronic pain were inadequately treated. However, at the same time the abuse and diversion of prescription drugs was increasing.

The initial label indicated that OxyContin is a Schedule II drug. The clinical trials section of the label described the result of several trials in patients with cancer and non-cancer pain, in opioid-naïve patients, and the results of open label

and equivalence trials.

Initially, OxyContin was indicated for the management of moderate to severe pain when an opioid would be required for more than a few days. The warnings, dosage, and administration section of the label cautioned against destroying the integrity of the tablets and informed that this can lead to the release of a potentially toxic amount of oxycodone.

Notably, the drug abuse and dependence section stated that the delayed absorption provided by the controlled-release properties of the drug is believed to reduce the abuse liability of OxyContin.

In 1996, the 18 milligrams strength was approved followed in 2000 by the approval of the 160 milligram tablet. The label was revised to reflect that this high strength should be used only in opioid-tolerant patients who require a total daily dose of a 160 milligrams or 320 milligrams.

Around the time when the 160 milligrams strength was approved and released, Purdue began an aggressive marketing campaign. Through considerable advertising and other strategies, the company

promoted the use of OxyContin, mainly among primary care providers as compared to pain specialists.

Purdue also promoted the use of OxyContin for non-cancer pain, including pain due to osteoarthritis and postoperative pain. Also, OxyContin was promoted as first-line therapy for chronic pain, which was inconsistent with pain treatment guidelines.

In May of 2000, the Division of Direct Marketing, Advertising, and Communications issued an untitled letter to Purdue regarding some of its promotional materials. The letter cited the company for making misleading efficacy claims inconsistent with the label, as well as safety-related text, providing incomplete information for the proper administration of the drug. Following receipt of the letter, Purdue ceased dissemination of these activities.

In that same year, the media in certain states began to report cases of abuse and diversion of OxyContin. The drug was being crushed and administered by oral and non-oral routes. As a

result, patients experienced adverse events or effects, including addiction and even fatalities. Also, worse was the fact that teenagers were part of the population abusing OxyContin.

There are several possible reasons for why OxyContin became a favored drug of abuse and diversion. A recent study suggests that oxycodone is more reinforcing than morphine. Of note, OxyContin has a higher oxycodone content compared to immediate release oxycodone. Also, in contrast to the initial belief that the pharmacokinetics of the controlled-release formulation would render the drug less abusable, more recent experience has shown that this isn’t the case, if the controlled-release properties of the drug are defeated.

An additional contributing factor to the increase in OxyContin abuse and diversion is the increased availability of OxyContin. With the emphasis on good pain management, prescribers have been more accepting of the use of opioids to treat pain. That, combined with Purdue’s push to promote OxyContin may have led to the increased availability

of the drug.

Finally, the product labeling could have been a factor. Warnings regarding the release of a high-dose oxycodone with crushing of the pill could have alerted some abusers to how they could misuse the drug. Also, the language about lower abuse potential of OxyContin may have misled patients and prescribers about the actual addictive risks of OxyContin.

Both Purdue and FDA took actions to evaluate and attempt to reduce the abuse and diversion of OxyContin. Purdue elected to discontinue marketing of the high-strength 160 milligram tablet. FDA experts were focused on reviewing all available data to look at OxyContin-prescribing practices as well as adverse events.

As part of the actions to reduce the abuse and diversion of OxyContin, the company and FDA also worked together to develop a risk map that included education and outreach, labeling, surveillance and intervention.

As a result of what was learned about abuse

and diversion of OxyContin, the agency decided to revise the product label. The revised OxyContin label was approved in July of 2001 and key changes were as follows.

First, a boxed warning was added that described the potential for abuse, misuse, and diversion of OxyContin and emphasizes the proper patients for treatment. The clinical trials section was restricted to the sole adequate and well-controlled trial, and the indications section was well written to specify the appropriate treatment population.

The indications section now stated that OxyContin is indicated for the management of moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time. The indications section also stated the patients for whom OxyContin is not appropriate, including those who need PRN or as-needed dosing and those in the immediate postoperative period.

The warnings section was expanded and rewritten with more prominent and detailed language

that cautions against destroying the integrity of the pills and describes the potential for misuse, abuse, and diversion of OxyContin.

With respect to the drug abuse and dependence section, the sentence implying reduced abuse liability of OxyContin because of the controlled-release formulation was deleted.

The agency held several advisory committee meetings to discuss the use of opioid analgesics in pain patients as well as the potential for abuse and misuse.

At the 2002 meeting, the opioid analgesic use, misuse, and abuse, as well as the use of opioids in pediatric patients was discussed. It was concluded that while abuse of opioids is a significant public health problem, these drugs are important for proper pain management. It was also noted that an overly-restrictive risk management plan may limit the proper use of these drugs in legitimate patients.

In 2003, the agency held another advisory committee meeting, this time to discuss risk

management plans in general and specifically one that had been proposed for Palladone, an extended-release formulation of hydromorphone.

I will abbreviate risk management plan as RMP in my talk.

At the end of the meeting, it was generally agreed that RMP should have the components of prescriber and patient education and surveillance of the drug misuse, abuse, and diversion, and should also assess the impact of opioid-prescribing practices.

The initial NDA application for the new OxyContin formulation was discussed at an advisory committee meeting held in May 2008. The committee concluded that tamper-resistant claims were not adequately supported by the available data. Also, a concern was expressed that inclusion of the new physiochemical properties in the label may result in false security and adversely impact the already-existing addiction and overdose problems. With regards to the RMP, it was recommended that it be directed to the entire opioid class.

In November of 2008, a meeting of the advisory committee was held to discuss another extended-release oxycodone formulation, Remoxy XRT. The inadequacy of data to support tamper resistance and false security from including the new properties in the label were discussed again. The committee also emphasized on the need to define minimum standards for assessment of tamper-resistant qualities.

According to Section 501 of the FDA Amendments Act, the agency has been granted authority to require risk evaluation and mitigation strategies, or REMS, for products when it is necessary to ensure that the benefits of the drug outweigh the risks.

FDA’s working on a class-wide REMS strength to include all extended-release and long-acting opioids. Until the class-wide opioid REMS is implemented, the agency has determined that extended-release opioids may be approved as long as the risk-benefit ratio is at least as good as already approved extended-release opioids.

As with the recent approval of an extended-

release morphine product, OxyContin would have an interim REMS should it be approved. The proposed interim REMS OxyContin will consist of a medication guide and a communication plan that includes Dear Healthcare Provider and Dear Pharmacist letters and a timetable for submission of assessments.

To summarize, the agency and Purdue have worked to strengthen OxyContin's product label and develop a risk management plan. Nevertheless, abuse and diversion of OxyContin continue to be a considerable public health problem. While it is desirable to have a less abusable controlled-release oxycodone on the market, the actual impact of this product abuse is unknown. Epidemiologic studies of abuse will be required to assess the impact of reported abuse-resistant formulations.

Thank you.

DR. KIRSCH: Thank you. Next will be Dr. Katherine Dormitzer.

DR. DORMITZER: Good morning. My name is Katherine Dormitzer. I'm an epidemiologist in the Division of Epidemiology in the Office of

Surveillance and Epidemiology.

Today, I'm going to present a brief summary of the presentations that were previously presented at the AC meeting that was held on May 5th. This presentation will include presentations that included data from SAMHSA, which is the Substance Abuse Mental Health Services, which would be TEDS, which is the Treatment Episode Dataset, NSDUH, which is the National Survey on Drug Use and Health, and DAWN, the Drug Abuse Warning Network, as well as previously-presented analysis on drug abuse ratios associated with OxyContin.

TEDS, otherwise which is the Treatment Episode Dataset, is a data system that provides descriptive information about the admissions from alcohol or treatment facilities that were publicly-funded. It collects annual data on the number and characteristics of persons admitted to these programs. And although information is available on the drug substance or class that was responsible for these admissions, only 16 states report on the specific opioid that was involved in this admission.

This slide shows that opioid analgesics were the primary substance responsible for admissions to a treatment program in 2006. It's 4 percent. And based on the 16 states that provided data on the specific opioid involved in this treatment admission, oxycodone was mentioned 15,000 times. And as you can see, the number of admissions for opioid analgesics began to increase after OxyContin was approved.

Now I'm going to just summarize the National Survey on Drug Use and Health. It's called NSDUH, and it was formerly titled the National Household Survey on Drug Abuse. And it provides reports on quarterly and annual estimates on the abuse of illegal drugs, alcohol, tobacco, as well as benign medical use of prescription drugs. And that's where this -- the question that they ask is, you know, did you take this drug that was not prescribed for you or you took the drug only for the experience or feeling it caused?

Here's a pill show card that respondents used to identify the pain reliever that they responded was used non-medically. and as you can

see, we have oxycodone products up there and then -- where are the OxyContins? Okay. Well, I lost them, but they're on this pill show card.

These are the estimates in millions of the non-medical use of pain relievers by type. This is a lifetime use estimate. So respondents may not have necessarily have used a substance in the past year. And as you can see, there were 4.1 million lifetime users of OxyContin specifically.

This slide presents past year use of OxyContin. And as you can see, there were more than 500,000 people in the United States that used OxyContin non-medically for the first time. That's the past year initiates. There were more than a million people who used OxyContin non-medically in the past year and this is by year, 2004 to 2006. And more than 300,000 people endorsed DSM criteria for dependence. Again, you can see it, 2004 to 2006.

This slide displays the percentage of people with drug dependence among past year users of each drug type. So for OxyContin, 5 percent of past year users responded with symptoms of DSM criteria

for drug abuse and 23 percent of past year users responded with symptoms of DSM criteria for drug dependence.

The Drug Abuse Warning Network, DAWN, is administered by SAMHSA and it's a public health surveillance system of emergency room visits and will provide national estimates on these visits.

Okay. I'm going to be providing estimates on the non-medical use of pharmaceuticals, which would be over here. And here, the confidence intervals help because when the confidence intervals overlap, then they're not statistically significant. And what you can see here is that the DAWN estimates for 2006 related to hydrocodone and to oxycodone overlap a great deal.

This is a presentation of the national estimates in DAWN on the extended-release formulations and the immediate release formulations. And again, you can see a fair amount of overlap in the estimates. These are visits in thousands, so 22,000 visits, 18,000 visits in 2004.

So now I'm going to be presenting on the

drug abuse ratios. So for the numerator data, I will be using DAWN, and for denominator data, I will be using drug utilization data and calculate estimates per 10,000 retail prescriptions.

Again, the numerator, these were the estimates that we saw for hydrocodone and oxycodone, and we saw that they were basically the same. And denominator, that's not what's shown. What's shown is that the number of hydrocodone prescriptions are significantly higher than they are for all oxycodone products.

Therefore, when you look at the ratios of ED visits per 10,000 prescriptions, the numbers for hydrocodone are remarkably lower than for oxycodone. But now what we're looking at is extended-release oxycodone products and immediate release oxycodone products and this is the numerator. As you can see, they're very similar, but the denominator, immediate release oxycodone products, is again significantly higher than the extended-release. And so, what we're seeing again is that the immediate release products here, the numbers of non-medical use per 10,000

prescriptions, is considerably lower than for the extended-release oxycodone products.

So there are limitations with these when we're calculating these estimates because they are different sampling methodologies, they are different populations, and the data are in no way linked. What this means is that DAWN does not have information on did the patient have a prescription to the drug that brought them to the ED.

So what we are seeing from TEDS, NSDUH and DAWN is that there is a significant public health burden on the non-medical use of opioids and specifically for OxyContin, and that even though the ratios appear to be stable, in other words the numbers per 10,000 retail visits appears to be fairly flat, the numbers of users are actually increasing because the numbers of prescriptions are also increasing.

Thank you.

DR. KIRSCH: Thank you.

We're now scheduled to take a break. The break will be 10 minutes in duration. Committee

members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:05.

(Whereupon, a recess is taken.)

DR. KIRSCH: I'd like to have everyone please take their seats.

I'd like to welcome the sponsor to the podium for their presentation. First for the sponsor is John Stewart.

DR. LANDAU: Good morning. I am Craig Landau. I'll be introducing John Stewart. But I wanted to thank everyone in attendance for inviting us here to participate. I'll be facilitating this morning's public session. I'll also be presenting some of the segments on the agenda.

Our president and chief executive officer, Mr. John Stewart, has some introductory remarks to make.

DR. STEWART: Thank you, Craig, and good morning, ladies and gentlemen. We appreciate the opportunity to speak with you today.

As Craig has said, I'm John Stewart, president and CEO of Purdue Pharma, and I assumed this role 15 months ago, but my experience with the organization goes back for many years.

I was previously head of Purdue Pharma in Canada, and prior to that, led the research and development activities in that country where I was closely involved with the development and registration of controlled-release formulations of morphine, codeine, hydromorphone, as well as oxycodone.

The majority of our presentation today will be led by our chief medical officer, Craig Landau, and Craig will call on several of our colleagues and two external experts who worked with us on the development of this new formulation. But prior to that, I'd like to just take a few minutes to give you some background on Purdue Pharma, the development of OxyContin, and our involvement in many activities that are designed to reduce abuse, misuse, and diversion.

Purdue Pharma is a research-based

pharmaceutical company and for the past 25 years has been one of the leading companies in the area of pain research. By far, our best-known pain products are MS Contin, a controlled-release formulation of morphine, and OxyContin.

Introduced in 1984, MS Contin was the first controlled-release opioid marketed in the United States, and it was widely recognized as a significant advance for the treatment of cancer pain. OxyContin itself was developed in the late 1980s and early 1990s, and since being approved in 1995 has been prescribed to millions of patients, providing relief from pain and improving the quality of many lives.

As we know from the history of the past years, unfortunately, OxyContin's delivery system can relatively easily be compromised and when that happens, overdose can occur.

As you know, OxyContin has also become a target of abuse by both educated addicts and recreational abusers, sometimes with fatal consequences. Accidental misuse by patients or caregivers has also been a real, if less frequent,

problem. And for these reasons, we are here to talk to you today about our efforts to reformulate OxyContin. These efforts reflect our appreciation of the deep sorrow that is caused by the loss of loved ones to drug abuse and at the same time the importance of providing therapeutic options for patients suffering from chronic pain.

Our aim is to introduce a new formulation of OxyContin, a formulation that has all the same efficacy as the existing product but with additional physiochemical properties to make it more difficult to certain routes of abuse.

We fully recognize, however, that a new formulation is not going to be possible to address all forms of abuse, and a new formulation, for example, cannot impact individuals who simply take a quantity of tablets and wait for the contents to be released over time. And for this reason, we see the introduction of this new formulation as only one element, albeit an important element, of the many activities to reduce abuse, diversion, and misuse.

It is our belief that through a variety of

activities, we can make a significant impact on the abuse of prescription opioids while at the same time not overly restricting the availability of these needed drugs for patients in pain.

As such, we are committed to pursuing a wide variety of actions to reduce abuse, including working with the FDA, key stakeholders, and other members of the pharmaceutical industry to develop a class risk evaluation and mitigation strategy to be applied to all long-acting opioids.

We'll also continue our long-standing support of community partnerships and anti-abuse campaigns and investments in activities to support law enforcement and crime reduction. We also have a number of other programs that Pamela Bennett will describe more fully in her presentation.

In closing, we've learned a great deal from our experience with OxyContin. We understand that while we manufacture and develop products to bring important therapeutic benefits to patients, those products carry real risks. Across our entire organization, it is our responsibility and commitment

to take actions to see that those products are appropriately prescribed and used as directed while at the same time mitigating against their risks of abuse, diversion, and misuse.

Thank you very much for your attention and now let me turn the meeting back over to Craig.

DR. LANDAU: Thank you, John. So here's how our public session is laid out for the rest of the morning. After some introductory remarks of my own, Pamela Bennett will provide a summary of some of the efforts Purdue's taking to address the abuse of our product and other opioids. We'll speak to polyethylene oxide, the primary excipient in the new formulation. We'll present data demonstrating bioequivalence of the reformulation to the current product, and we'll hear from one of our external experts, Dr. Ed Cone.

Dr. Ed Cone will describe the approach we took with his assistance and other experts in designing our in vitro testing program. One of my colleagues from Purdue will present representative and properly-redacted summary methods and results,

and another one of our external experts, Dr. Ed Sellers, will provide his interpretation of the results of these in vitro studies and his view of the potential impact the reformulation can make in multiple settings.

I'll conclude with some remarks on what we understand about the reformulation and why we believe we should be transitioning to the new formulation in the marketplace just as soon as possible.

Now, it's important to start with what's relevant for our development path here. As John mentioned, this product, the original formulation and the reformulation, are developed for patients. Over one million patients every year are treated with OxyContin and they use it to effectively manage their pain and maintain a certain quality of life.

The current product has a specific vulnerability and it's well understood by all of us. It can be easily crushed within a matter of seconds with no more than a bottom of a glass or two spoons, rendering all of its oxycodone immediately available, whether this is an intentional act or an inadvertent

one.

This is what makes it attractive to abusers who seek to manipulate the tablets for a rapid or fast high or what makes it dangerous for experimental abusers, including teenagers who might receive the product in a schoolyard and be told to crush it or chew it. This is why we reformulated the product and this is why we're here today to speak about it.

Now to understand the potential value of the reformulation through the in vitro experiments we've conducted, it's important to understand how the current product performs when taken as directed into an intact form. And we can see this in results of standard dissolution testing.

What I have here plotted on the vertical axis is percentage of oxycodone released from a current intact OxyContin tablet. It's plotted over time on the horizontal axis, and what's obvious is that over 12 hours, all the oxycodone is released. This is how it becomes therapeutic for patients.

Now this picture changes dramatically when the tablet's crushed. Something I mentioned a moment

ago, it happens quickly and easily in a matter of seconds. And here you have a picture of a crushed OxyContin current tablet. If you can't make out the resolution in the back, it resembles bleached flour. It's a fine series of particles. This is all oxycodone and excipient.

Here are the corresponding dissolution profiles for tablets manipulated with a pill crusher, a mortar and pestle, or even two spoons from a kitchen cabinet. What's obvious here through analysis of the first 60 minutes is that all of the oxycodone in a given tablet is available within 5 to 10 minutes. Again, this is why we reformulated and this is why we're here to discuss it.

We understand that with the exception of swallowing, which is another substantial route of abuse, swallowing of intact tablets, crushing underlies the abuse and misuse of OxyContin through many routes of administration, oral administration, snorting, rectal administration, smoking and, of course, intravenous injection, a very dangerous practice. It's also a precursor to further chemical

manipulation for the purposes of extracting drug from the tablet.

But the importance of crushing, where the relevance is not lost simply on abusers, it's also relevant for patients in the context of medication errors. We understand this occurs. We have reports of this in our database and FDA has reports of it in their reporting system.

Inadvertent crushing or chewing by a patient or administration of a crushed tablet by a well-intended caregiver is something that occurs. And although it doesn't involve crushing or manipulation, another important question to ask ourselves is, is this new formulation sensitive to the effects of alcohol? Does it dose dump in alcohol when a patient might inadvertently administer, self-administer the tablet along with a beer, wine, or even a cough suppressant at night.

So we started to address these issues through reformulation as far back as 2000. We used multiple technologies and formulation platforms. We conducted multiple in vitro experiments, non-clinical

experiments, and even in vivo studies to assess a variety of formulations that could help to address the problem I just presented.

Ultimately in 2004, we began focusing on the formulation we're talking about today. It's a single entity, controlled-release formulation of oxycodone that utilizes a different primary excipient, polyethylene oxide. We'll speak about it in a little while.

In November 2007, after discussing the elements of the development plan with FDA, the Review Division, we filed the initial NDA. The NDA included data supporting the bioequivalence of a subset of the tablet strengths, 10 through 40 milligrams.

In May of 2008, we participated in our first advisory committee meeting for this formulation, and later that year, in October, we received a complete response letter. The formulation was not approved.

In March of this year, we resubmitted the NDA, this time with data supporting bioequivalence of the remaining strengths, the 60 and 80 milligram

tablets, and also data from a comprehensive in vitro testing program that very clearly demonstrate the physiochemical differences between the reformulated product and the product it's intended to replace. Of course, we're here today in our second advisory committee and we're looking forward to a productive discussion.

Now to make certain we designed and conducted experiments that were sensitive to the comments and the suggestions received from the advisory committees and from FDA, we consulted experts in abuse and tablet manipulation.

Two of these experts are here with us today. They'll be presenting a little later on in the public session. These are Dr. Ed Cone and Dr. Ed Sellers.

Based on their input, the input of the combined advisory committees, and specific guidance from FDA, we've modified our approach in three very important ways and it's very important everyone understands this.

Of course, we've submitted results from a

comprehensive in vitro testing program demonstrating a clear incremental improvement upon the current formulation.

Since we've reformulated the remaining strengths, we're now in a position to introduce all of them at the same time. And, most importantly, our proposed package insert includes no reference to tamper testing, in vitro data, tamper resistance, abuse resistance, or abuse deterrence.

I'd like to pause for a moment before moving on with the next portion of our agenda, as I think it's very important that we're clear.

Unless and until post-marketing epidemiology data support it, Purdue will not and cannot assume and promote that the reformulation carries any less abuse liability than the current formulation.

Our next speaker is Pamela Bennett. She'll be speaking to some of the efforts Purdue has undertaken to address the opioid abuse problem of OxyContin and other drugs.

Pamela.

MS. BENNETT: Thank you, Craig.

Good morning. My name is Pamela Bennett. I'm a registered nurse and the past president for the American Society of Pain Management Nursing. I've spent my career caring for people with pain, be it at the bedside, in management, as an advocate, or in my current role with the company. This is my life's work.

Shortly after joining Purdue in 2001, I became involved with several of our company's efforts to address prescription drug abuse. We recognize, both as individuals and as a company, the tragic consequences that can result from the abuse and misuse of prescription medications.

While we are here today to discuss the new formulation of OxyContin, we recognize that there's not one single solution to combat the problem of prescription drug abuse. And that is why we are partnering with numerous stakeholders, including industry, government, law enforcement, healthcare professionals, patients and communities to address this problem.

We recognize these efforts cannot be fleeting and they will require sustained attention and commitment on the part of all people involved, and Purdue is committed. And today I'm going to highlight just a few areas in which we've been active in this area.

Our efforts have encompassed national initiatives to detect abuse and diversion, encouraging states to enact effective prescription monitoring programs, as well as efforts to educate local law enforcement, healthcare professionals, and communities.

One of our major efforts was the creation of the RADARS System. In direct response to the abuse problem in 2001, Purdue convened an advisory panel of external experts to develop a timely and geographically-specific monitoring program to detect abuse and diversion of opioid analgesics.

The RADARS System draws together the broadest range of early warning systems, providing stakeholders with a first alert for significant changes in abuse trends. As you know, in 2006 Purdue

transferred ownership of the system to the not-for-profit Denver Health and Hospital Authority, which now owns and operates it independently.

Supporting appropriately-designed state prescription monitoring programs is another one of our national efforts. The goal of these programs is to identify, deter, and prevent drug abuse and diversion while supporting access to the legitimate use of these medicines.

One example of what a PMP can do is it can help identify those individuals who are doctor shopping or are going to multiple prescribers to obtain multiple prescriptions.

Again, early on, since October of 2001, Purdue has supported the development and passage of state legislation to adopt appropriately-designed PMPs. We continue to partner with state health departments, licensing boards, and professional societies to promote the use of this program. To date, 40 states have enacted legislation in this area. We also recognize the importance of education at the community level and we're engaged with a

variety of efforts with law enforcement, healthcare professionals, and the public.

Purdue's law enforcement education and liaison program, which is staffed by drug diversion experts, provides education and technical assistance to law enforcement agencies to help them effectively combat drug diversion. The program also helps healthcare professionals recognize and prevent attempts by diverters to inappropriately obtain controlled substances.

This effort is in addition to our ongoing commitment to healthcare professionals in their education. We make unrestricted educational grants to accredited providers of medical education, such as hospitals and academic institutions. The funded programs have reached over 1.2 million healthcare professionals.

We have also engaged with community organizations and individuals across the country to raise awareness about the dangers of prescription drug abuse, and I'd like to just share two brief examples.

Since 2001, we've been working with national drug abuse organizations, such as the Partnership for Drug-Free America, and with local community coalitions to raise public awareness of the problem.

In 2002, Purdue created the Medicine Cabinet Public Service Campaign to educate the public and communities where abuse was a particular problem about the importance of safeguarding medications in the home. The picture seen here is what is present in the newspaper ad that we run.

Prescription drug abuse is a serious problem. And as I can tell you as a mother, I worry about the welfare of my daughter, and I would do anything I could to protect her and to keep her safe. I've spoken to parents who have lost a loved one to overdose and I can't even begin to imagine the depths of the grief and loss that they experience.

We are committed to combat this problem, to help prevent needless tragedies that result from the misuse and abuse of these prescription drugs.

As a nurse and a caregiver, I also know the

burden that pain has on our society and the impact it has on patients and their families, the day-to-day moment-by-moment struggles that many of these people suffer. Many lose their ability to enjoy life or to work. Most become isolated. Several lose their families and, unfortunately and tragically, some lose their lives.

Managing people's pain provides an opportunity for people to have their life back. And I can tell you there's nothing more rewarding than to help someone go back to work or to be able to hold their child or to be able to find joy in the simple things that make life meaningful for all of us.

I believe that as a society we must do whatever it takes to ensure that people with pain have effective access to appropriate and effective care.

My hope is that, as you consider the science of what is being presented today and the very real and significant problem of prescription drug abuse, that you will not forget and that you will remember the needs of the very patients that we

strive to serve.

Thank you.

DR. LANDAU: Okay. Before we move on to present data demonstrating bioequivalence of the reformulated product to the current formulation, I thought I'd speak just a few minutes, short minutes, a bit on the formulation's primary excipients, since it's new, to the formulation, polyethylene oxide.

Polyethylene oxide is inert and it's found in a great many foods and pharmaceutical agents. It's an ideal excipient for us in this formulation because when subject to a specific manufacturing process, it confers hardness to the tablets. And based upon its underlying properties, it hydrogels in small volumes of water, and you'll see this in a few minutes. It was this absorption of water that allowed us to create this bioequivalent formulation to the current product.

So here's the structure of polyethylene. Polymers, containing multiple subunits of this structure, are distinguished from one another based upon the number of times the subunit repeats and,

hence, its molecular weight. Polymers with less than roughly 2,300 repeats of this structure or a corresponding molecular weight of less than 100,000 are generally considered polyethylene glycols or PEG, very common component of many medications that are currently marketed. They exist as liquids to waxes.

Polymers that have more than 2,300 repeats of the structure are considered polyethylene oxides. They exist as waxes, waxes to powders. You can see a white dot on this arrow represents the specific molecular weight of the polyethylene oxide used in this formulation.

I mentioned polyethylene oxide is not new. It’s found in many pharmaceutical products. We’ve listed just a few of them, a handful here. These are over-the-counter medications, some of which are indicated for the treatment of children. They’re mostly cough suppressants or cough/cold medications here, but it’s also a well-known component of a variety of prescription medications, including some that have been marketed for 20 years or more and used in the treatment of millions of patients.

So there are three important components or factors to keep in mind throughout the public presentations and the discussions that follow regarding polyethylene oxide.

Its slow uptake of water makes it an ideal excipient to be used in controlled-release formulations like OxyContin. Its hydrogelling properties in small volumes and the hardness it confers when subjected to a specific manufacturing process make it an excellent choice to make tablets harder and more difficult to manipulate. And, finally, as I mentioned just a moment ago, its longstanding track record of use in multiple pharmaceutical products and foods assures us that it’s a safe excipient to use.

With this, we’ll begin our presentation of data. These are data demonstrating bioequivalence of the reformulation to the current product, and for this I’ll call on Dr. Stephen Harris, who heads up our Clinical Pharmacology Department at Purdue.

DR. HARRIS: Thanks, Craig. Before briefly reviewing the design of our bioequivalence and dose

proportionality pivotal studies, I'd like to spend just a moment reviewing some of the terms that provide a context for the conduct of these studies.

Bioequivalence is the demonstration of the absence of a major difference, in this case, of oxycodone exposure. And bioequivalence is assessed statistically by standardized FDA methodology that's been promulgated in various guidance documents and has been in successful use for over 20 years.

The essence of this statistical testing is establishing 90 percent confidence intervals for the relevant pharmacokinetic comparisons and demonstrating that those 90 percent confidence intervals lie within the defined acceptance range of 80 to 125 percent.

Therapeutic equivalence, as Craig mentioned earlier, was the goal of our reformulated product in order to ensure that it will deliver the same safe and effective treatment to patients when taken as directed, and bioequivalence provides the support for that through the determination that in fact oxycodone exposures are similar.

Bioequivalence testing involves a test formulation. In today's case our reformulated OxyContin product is the test formulation and a reference comparator, in this case the current OxyContin formulation.

Bioequivalence determinations are commonly used in drug development. They underwrite the approval of generic drugs. They are also used in new drug application contexts. For example, when a sponsor changes a formulation slightly between Phase III pivotal studies and the introduction of a commercializable dosage form, demonstration of bioequivalence allows therapeutic equivalence between those two related formulations to be established.

In addition, bioequivalence studies are used in a post-approval setting, such as the one before us today, where a formulation change, a manufacturing site change, an excipient change, or other change requires a demonstration in human beings of the comparability of exposure to the active pharmaceutical ingredient.

We have conducted six pivotal

bioequivalence studies and two pivotal studies to assess dose proportionality. I'd like to begin to explain the bioequivalence studies by showing the three tablet strengths at which these studies were conducted. We have the 10 and 80 milligram strengths, which are respectively the lowest and highest tablet strengths for both the current OxyContin formulation and the reformulated product, and we also studied the intermediate strength of 40 milligrams.

At each of these three tablet strengths, we conducted paired studies under fasted conditions as well as under fed conditions. And this is consistent with FDA guidance regarding modified-release products where one needs to study them -- in addition to the fasted state, to study them in the fed state where administration of a standardized high-fat meal stimulates the various physiological and chemical changes in the gastrointestinal tract that may produce a lack of comparability.

In the middle we have features that are in common to all of the studies we've conducted. They

were randomized open label single-dose comparisons using healthy male and female subjects under naltrexone blockade.

The design of the BE studies in particular is the standard design two-way crossover studies with the reformulated OxyContin as the test product, current OxyContin as the reference product.

On the lower portion of the slide we see the two dose proportionality studies. These are studies of the reformulated product intended to demonstrate that the exposure to oxycodone that results is proportional to the amount of oxycodone contained in the tablets, and the design of these studies was as appropriate to the number of tablet strengths that were studied in each of those.

Now I'd briefly like to review the results, and I don't expect anyone to look at all these numbers, but this table is of the six bioequivalence studies, one study per row in the data section. And I'd like to draw attention to the critical statistical evaluation.

These are the 90 percent confidence

intervals for the key pharmacokinetic comparisons of Cmax, the maximum exposure to oxycodone, and AUC infinity, a measure of total exposure to oxycodone. And the regulatory standard for bioequivalence is that these 90 percent confidence intervals lie within the 80 to 125 acceptance region. And as you can see in each case for all six studies and for both metrics, the confidence intervals are well within that acceptance region.

Shown below, briefly, are the results of the two bioequivalence studies. There's an analogous statistical procedure to establish dose proportionality. And these two studies have demonstrated that for the reformulated OxyContin product, the exposure to oxycodone is proportional to the tablet strength.

I'd now like to show the mean concentration versus time profiles from some of these studies. In particular, this is the 10 milligram tablet strength in the fasted state. The curve here is following single doses administered at time zero with a 72-hour X axis; on the Y, or the vertical axis, concentration

of oxycodone. The blue line with the hollow circles is the current formulation. The red line is the reformulated product, and you can see they're performing similarly.

These are the same plots now for 10 milligrams in the fed state. And then at our top tablet strength of 80 milligrams for the two products, here are the comparative mean concentration versus time profiles for 80 milligrams in the fasted state and, finally, for 80 milligrams in the fed state.

So taken together, these studies demonstrate the therapeutic equivalence of current OxyContin and the reformulated OxyContin demonstrated by fed and fasted bioequivalence at 10, 40 and 80 milligram tablet strengths and also demonstrate dose proportional oxycodone exposure for the reformulated product over the full range of tablet strengths from 80 down to 10 milligrams.

Thank you.

DR. LANDAU: Okay. I had mentioned earlier on when we reviewed the agenda that we'd be joined by

two external consultants, the first of whom is Dr. Ed Cone, who advised us specifically on how best to design our in vitro studies so that they would reflect real-world tablet manipulation scenarios that exist today and might exist in the future.

So Dr. Cone.

DR. CONE: Well, good morning to all of you. I'm Ed Cone. I'd like to start out by just saying thank you for your time that you're investing here and the opportunity to speak to you.

I'm going to try to briefly explain my role in helping Purdue Pharma develop laboratory methods for the tamper assessment of their new reformulated product.

We basically had two missions in mind that we had to do and one was to look and identify what people were doing to current OxyContin, but not only OxyContin, other opioid formulations, in terms of manipulating and changing the formulation from a controlled-release-type formulation to an immediate-release formulation, and then to translate, and it's not always easy to do, those real-world scenarios

into systematic rigorous scientific studies.

Before I go into any basic detail, though, I just want to give you a little bit of background on who I am and how I fit into the picture.

I obtained my Ph.D. in organic chemistry from the University of Alabama, my home state. I'm always proud to get that in. But I did postdoc at the University of Kentucky studying tobacco alkaloid chemistry.

I then joined the Addiction Research Center in Lexington, Kentucky, which ultimately was assimilated into the National Institute on Drug Abuse, NIDA. And that was an extremely rewarding experience to be a researcher in the clinical program at the Addiction Research Center, which ultimately then I spent 12 years there. And then ultimately they moved the center to Baltimore and I started up the clinical research program in Baltimore at that point. And I spent another 14 years in Baltimore.

It was quite an unusual experience for a research chemist to be able to work in the clinical program. I worked for the entire 26 years almost on

a daily basis in being able to talk to and interact with drug addicts. These were volunteers in the program and I was always very conscious to show them all the respect. These were just people like you and I but had taken a different course in life in terms of their drug use, but they were making an incredible contribution to the program as well.

But in those conversations, those many, many, many hours that I spent in conversation with them, I was very interested in understanding the whys and wherefores and hows of their drug abuse behavior and habits. Why was it important? To me it was important to understand because that was the real-world thing, and I could take all of that knowledge back to the laboratory and try to translate that into reproducible laboratory assessments of the pharmacology and the chemistry of drugs of abuse. So it was an incredibly rewarding experience and, of course, over the years I've published extensively on my studies.

I retired from NIDA as a commissioned officer in 1998 and joined Pinney Associates as a

consultant and have worked since then with Pinney Associates.

Just very briefly, Pinney Associates is a consulting firm in Bethesda, Maryland, and they specialize in pharmaceutical risk management, issues management. They also have a very strong expertise in abuse liability assessment.

So with that as background, I also should provide you with some disclosure of my status, my relationship with Purdue. I appear today and have worked with Purdue as a consultant from Pinney Associates. Pinney Associates gets paid for my time and I should also mention that the opinions I express are my opinions, and not those of Purdue and not those of Pinney Associates.

So our basic job in developing laboratory experiments was to first identify what is happening in the real world with OxyContin and other opioids, and I thought the place to start was to understand at least some of the information that was available on routes of administration.

So the next slide I'll show you -- oh, I'm

sorry. Before I go on, I wanted to briefly outline the work I've done over the past year or so with Purdue just to give you a little bit better feel.

I've served on any number of their committees in identifying routes of administration and types of abuser behavior that are pertinent to manipulation. I've served on all of the three committees. The goal of these committees, of course, was to develop laboratory assessment methods based on real-world scenarios.

I'm the one that went out to the third party laboratories that were performing most of these studies under blind conditions and checked them out and looked over their shoulder and to see how they were doing it.

I also wrote sort of a chapter as part of Purdue's NDA filing on tamper assessment, and I think I was asked to do that basically because I had published a review way back before I started work with Purdue, back in 2006, on tamper assessment methodologies across many, many different types of pharmaceutical drugs and that was published in *Drug*

and Alcohol Dependence. So I've been heavily involved since 2008 in this reformulated project.

Now to get back to the theme in mind, how did we develop these laboratory tests. And as I said, the route of administration was the place I thought we should start. So we started with looking at what was known and this is one study. There are three or four studies now that tell us some detailed information about OxyContin and its relationship to some other drugs, as well, but primarily OxyContin and how it's abused in the real world.

This is a study by Katz, et al., in 2008, where he surveyed people on the Internet who were primarily recreational drug abusers about their mode and behavior and use of OxyContin. And this illustrates the most prevalent routes of administration. And, as you'll see, insufflation, or snorting, came up as extremely high prevalence. It's the highest one there, followed by oral.

This is intact drug use of OxyContin. But chewing came in third, smaller numbers of injection, and occasionally a few people would mention smoking,

but certainly snorting, insufflation, and chewing were very prominent in this study.

A second study or series of studies for additional information on OxyContin is shown in this slide. And what you see here, this is a little study that I did back in early 2009, another Internet study to get an update on what people were reporting on OxyContin. And again, we saw insufflation and snorting is the primary route that we're seeing or hearing from recreational users. But we also hear -- they reported in this case, this is primarily or all the oral route, is all chewing, and occasionally that chewing is combined with making an oral solution and drinking it. And again, IV use is relatively low in this population, but it is there, and we even see occasional weird routes, like rectal administration.

Now, if you look at the study on the right-hand side, this is a bigger study by Carise, et al. in 2007. And this is a different population, very distinctly different population. These are hard-core drug addicts who are entering drug treatment. And you see a very different-looking pattern, but it's

primarily now in addition to other opioids that they use. They report using OxyContin by the oral route. Unfortunately, she didn't differentiate whether it was chewed or intact. Most likely, it's a very healthy combination of both. But you see also IV use now has virtually doubled in this population and insufflation is also used but considerably less than in recreational.

But what these studies and some other data told us was clearly there's three important routes. And it's insufflation or snorting, it's oral, frequently chewing or oral solution, and, to a lesser extent, IV use. So that sort of characterizes the problem.

From there, we had to, I thought, go to, okay, so we know a little bit more about the problem, how do we translate that into solid science.

So the first thing we started out with was looking at manipulations; what's reported, how is the tablet done, various things. And certainly, the first one is physical manipulation, physiochemical processes that you can reduce the formulation into

something, and that's illustrated here. And this comes from a huge amount of my reading the Internet and talking with subjects and so forth. But, basically, they like simple tools. They like simple formulations to be able to crush a tablet by various means. And they report use of all sorts of little simple household items, like scrapers, grinders, cutters. Some of them also mentioned mortar and pestle. Okay. That's getting a little bit more in the chemistry area that I'm more familiar with, but they certainly are very familiar with the use of the mortar and pestle, and they're very familiar with the use of pill crushers, and you can buy a variety of them off the Internet or even from your pharmacy. So they've gotten that far and those are the simple tools. Very few go on to more sophisticated methods but occasionally you'll see a little bit of that.

So the yellow line is where I put about 90 to 95 percent of the entire population of people that tamper with opioids and specifically with OxyContin, they fall into this group of fairly simple tools. And the primary aim, of course, is to get it reduced

down to a powder, and from a powder they can do a lot more things with.

They can extract it for oral consumption. They can extract it for IV use or if they've got a fine powder, they can snort it, which is all three of those routes are important. And if they snort it, they generally like nice fine powder.

So what are the most prevalent things that people do? It's simple things. It's simple aqueous extractions again as illustrated here. This is where again 90-95 percent of the people are reporting what they do, both on the Internet and talking with them, but you do see some detailed recipes. They're pretty sophisticated, even from a chem standpoint.

I don't put those as being very prevalent, but they are there. Some people do them, and they involve some degree of training, resources, and skill. You see all sorts of recipes that involve use of alcohols or acids, somewhat advanced solvents, all sorts of interesting discussions on the Internet about effects of pH, what's the best solvent, all sorts of things, and how to purify it and isolate it.

Again, you see that. My thought is that that's in the very small percentage but it's there. So we have to evaluate those things.

Putting those physical-chemical processes together, I think then we get a much better assessment of what people are doing in terms of crushing, swallowing, insufflation, and injection, and occasionally a little bit more bizarre routes, like smoking which is rarely reported, and occasional rectal use.

So with this thought process in mind, I also wanted to at least talk to Purdue and tell them about

-- and fortunately we had a formulation that had some of these characteristics. But I, over the years in talking and learning about tampering practices, came up with at least three processes that really affect tamperability.

This is a snippet, but I've seen these hundreds and hundreds of examples of these types of reports. The average tamperer, if there is such a thing, the person who wants to manipulate a product

to get it reduced down to a powder, really hates those formulations when they come out that are extremely hard to crush.

This is just an example. This guy, he's pretty frustrated. He's talking about the tablet that's definitely not in any crushable form, and he goes on to say what else you can do with it. But he's really frustrated. He says put it in a glass of water and wait for it all to be released, but it'll take you about as long as if you just swallow it. So he's really frustrated with the hardness of the tablet. That's a good thing. That's what I've been telling every drug company I've talked to over the years. This is a good thing.

Another commonly-recurring theme that's reported over and over again is those formulations that, if they try to hydrate them, they turn into a sticky viscous mass. And you'll hear some discussion of the current formulation involves a lot of these things as a reason for discussing it. But these are good things to have.

Here, you'll see another snippet from this

person who says, “Don’t snort this stuff. You’ll be pulling massive amounts of thick sticky gel out of your nasal cavity.” So he’d successfully reduced it to powder, and he had snorted it, but he didn’t like the effect.

And finally, a more subtle concept that’s important, though, I think in consideration of designing a good formulation, is the idea of work. How much work does it take the person to get from point A to point B a crushed or extracted product, and that involves time, resources, skill and so forth. So the concept of work is there. And just to illustrate it, a little snippet here says, “I don’t know, man. Seems to gel more. Waiting two to four hours for it to seep into solution on a hot plate stove might work. This is a lot of work.”

So those three concepts in mind are part of the milieu of thinking in how to approach a formulation.

So with those in mind, this comes almost exactly out of my review back in 2006, and I think these principles still hold true today. This is what

I enunciated in this review that I had sort of gained from this knowledge of reading and reviewing and talking with so many drug abusers who were tampering with the products.

What it basically says is that although there will be a few of these people who take these detailed recipes and work and work and work on them, that's going to be in the very small minority of folks that are tampering with these products. Most people want fast, easy methods. And why? Because they want a bigger dose and a faster high and they don't want to spend a lot of time doing it.

So if you can put that barrier, that resistance barrier, or could call it work function into your formulation, so much the better, and as the work requirements go up, in my opinion, the frequency of tampering will go down.

So with all that in mind, here's how I advised Purdue. We had to take all of this knowledge base that we had about tampering methodologies and identify them. And something incredibly important and challenging was that not only do we have to look

at the way OxyContin is currently abused -- because it’s easy. I could abuse it; anybody can abuse it, can crush it down to a powder in a matter of seconds with anything you got on the table in front of you.

So we couldn’t limit our scope to those easy things. We had to reach out to other opioids and to other possible things that haven’t even been described yet, and that’s a pretty important and difficult challenge.

So when Purdue asked me did I have any ideas about all of that stuff, I said, oh, man, do I have ideas. We went over them and our goal was to translate those ideas and knowledge into systematic rigorous scientific studies. And along the way it was fun for me because I had input on virtually all of the methodological details, the number of replicates that needed to be done and so forth. But the best thing that I had going for me was I got to challenge the product in the lab myself, and I got to think up all these weird things that people might do, and then they had to test them out. And it was kind of neat.

When we put all this together, I think you'll see that Purdue designed a whole series of rigorous scientific studies that are representative of real-world scenarios. And I've listed the things that I was interested in making sure they did and they were in total agreement with all of these things, that we didn't just test one dose strength, we tested all dose strengths in virtually almost all of the experiments. If we didn't test them all, we bracketed them. Most of them involved testing all dose strengths.

I didn't want to stop testing at 10 minutes or 60 minutes or even an hour. One of my philosophies in helping them and working with them, and they listened, was we want to make it fail. We want to see where it fails. If we don't, you're going to be asking those questions; if you kept on doing this, what would have happened? So my philosophy was we keep on doing it. And if we can make it fail, we will make it fail and then define those conditions.

So to make it fail, we had to involve a lot

of different things. We didn't always -- we weren't very successful in many cases. But to make it fail, we had to cover environmental things, like high temperature, low temperature, the possibility of freezing, what happens in a microwave, all sorts of things.

We extended the time frame way out beyond 12 hours. Virtually all the experiments went almost to 24 hours or more. We had to have appropriate controls so that once we got a result, what do we compare it to. Our primary control was OxyContin, but we had to use other controls, as well. We had to do a sufficient number of replicates to make it a valid experiment and assess what's the variability in this process. Validated methods, of course, are required. And finally, independent laboratories under blind conditions and those folks at the laboratory were working with coded samples.

So to sum it all up, this incredible resource of information does have real-world significance in looking at how people actually do it on the in vivo side. It has aspects that describe

all sorts of things, like powdering, what happens when you swallow it, effects of alcohol, from simple to complex extraction methods, can it be pulled up in a syringe, all sorts of things.

When you hear the next speaker, I think you'll be relatively impressed by the incredible amount of work and hopefully the quality of the data that's available.

Thank you.

DR. LANDAU: Thank you, Dr. Cone. Our next speaker is Dr. Judy Lee. She's a colleague of mine from our Analytics and Preformulation Development Area. She's going to present to you appropriately-redacted summary information on the methods and resulting data from our testing program.

DR. LEE: Thank you, Craig.

Good morning. Underlining our tamper-testing protocol, we have three important goals in mind. First, we want to characterize physical-chemical properties of the reformulation. We want to compare the performance of the reformulation to current formulation, and we also want to test both

formulations to complete failure.

In designing, we got input from experts for real-world extraction of oxycodone for abuse. We also tested different lengths of time, effort, and special equipment required in order to reduce the particle size. We want to ensure all our studies are scientifically robust.

In designing, we have to consider all routes of real-world manipulation. As is shown here that you have seen before, here is a list of real-world tablet manipulation scenarios. We take each scenario and convert them into a specific laboratory procedure. It becomes our Studies 1 through 5.

Now before we start testing in the laboratory, we need to make sure the data we generate are meaningful and robust. We want to determine the number of replicates that are needed to conduct each test. So guided by our internal experimental data, we want to produce results with observed mean within 10 percent of the true mean at 95 percent confidence.

Guided by this statistical approach, we determined the appropriate number of replicates for

reformulated OxyContin. For example, N should be 5 for a small volume extraction. For current OxyContin, on the other hand, it's reduced to fine powder quickly, therefore N equals 3 is appropriate.

Now I want to show you a schematic design of one of our small volume extractions to illustrate our approach. Here is an example using a simple solvent one. First, we start with a whole tablet, in this case showing you here is a 10 milligram reformulated OxyContin.

Each test we conduct at two temperatures to understand the heating effect. With each temperature, we study six particle sizes from largest to smallest. With each particle size, we generated extraction kinetics at various time points. What we show you here is from 10 minutes to 24 hours. This is a study for all seven strengths and each test was conducted five times. This one design is encompassing more than 2,500 data points.

Now we also want to make sure the data generated is independent and unbiased, so all the studies were outsourced to contract research

laboratories. We conduct the development and validation internally. Once that's completed, we transfer the testing methods to CRO. The analysts at CRO were blinded to samples to the extent possible.

We have also external experts that conduct a site visit to make sure the procedures were conducted properly. Then at the end we have externally conducting the quality assurance and statistical analysis with all the data generated.

Now let me discuss Study 1. We have two goals we want to achieve for Study 1. First, we want to simulate expected abuser approach intentionally to crush a tablet for further abuse. Secondly, we want to understand the likelihood that a tablet can be accidentally crushed by patient or intentionally crushed by well-meaning caregivers.

Here is how we approached the Study 1. First, we need to identify tools to be used to crush hard substances. This is because reformulated OxyContin tablets are hard. We identified 16 common household tools that broadly represent all possible ways to reduce tablet sizes.

We evaluated different amount of effort and time with all the 16 tools. We identified a broad range of particle sizes from largest to the smallest. Then we divided this whole range of particle sizes into six distinct particle size bands. Then we used the standard laboratory equipment to reproduce those bands for further testing.

As I said, the reformulated OxyContin are hard. Let me show you the results generated with those household tools. On the left-hand side I'm showing you the 16 tools we used. When you apply these tools to current OxyContin, you get only one form; only fine powder was produced.

When you use the same 16 tools for reformulated OxyContin, here is what you will see. Indicated by the axis, most of the tools does not have any effect on OxyContin reformulated. The few that does work, it creates fragment, slices, or granulated particles, never fine powder. So we can conclude from our study current OxyContin tablets are crushable. It has a binary effect, either whole tablet or fine powder.

Reformulated tablets are hard. It takes time and effort in order to reduce their size. Even if you find a special tool, it has a graded response. Many household tools do not work on crushed reformulated OxyContin.

Now let me discuss Studies 2 and 4. Our goal for Studies 2 and 4 is to simulate a scenario of an abuser attempting to extract oxycodone from intact or crushed tablets in small volume of liquid.

Here is how we approached these two studies. First, we need to perform extraction. We choose 30 ml because it’s equivalent to an ounce, bar shot that can be easily drinkable. We have three type of solvents we investigated. Each solvent was conducted at two temperatures. As I said, we want to understand the heating effect. And every study is conducted with constant agitation at 100 rpm. At the end, we determined the amount of oxycodone can be extracted at various time points, including those listed here.

It’s very important to make sure our selection of solvents are proper. We want to cover a

wide range of chemical properties. Here, we consider three most important characteristics that define solvents. They are polarity, ionic strength, and pH. We cover the widest range of these three characteristics. With the help of experts, we came up with the list of solvents shown here. They include six simple solvents that's ingestible, three advanced solvents that's non-ingestible, and we have four buffers that cover a range of pH.

Let me show you some of our study results here. This is a complicated slide. Please allow me a moment to explain. On the left-hand side is showing you the three classifications of the solvents we discussed and the list of solvents within each classification. Across the top is showing you extraction time from 10 minutes to 18 hours. Right below that is particle size band covering large, medium, and small that we used.

The number in the slide is a percentage. It's the amount of oxycodone that's released on reformulated OxyContin related to current OxyContin. So these are percentage numbers. So you can see 100

meaning the same quantity is released. When it's less than 100, as we show here, 53, for instance, for simple solvent 1, medium particles at 10 minutes, that means 53 percent oxycodone released from reformulated as compared to current.

Now let me first discuss the data generated under 18 hours. You see a lot of high ratios. This is understandable. This is 12-hour product. At 18 hours you expect everything should have been released. Therefore, we did not conduct statistics on data generated at 18 hours.

We evaluated data generated at 10 minutes and 60 minutes since these time points are more relevant to the abusers. We conduct statistical analysis on all the data generated here. Let me first show you those two data points here, 100 for simple solvent 3, 99 for advanced solvent 1. These are the two data points with showing no significant difference between the amount of oxycodone released from reformulated versus current, which means the rest of the data points, they are statistically significant.

Let me highlight for you the two data points that's in the bottom of the slide here for advanced solvent 3. These two data points are shown statistically significant that more oxycodone was released from reformulated OxyContin. That means the rest of the data points, the vast majority here, are significantly different than oxycodone released from reformulated OxyContin are lower, slower than current OxyContin.

Now let me explain these two data points, 123 and 127, why we are not concerned. This is because advanced solvent 3 is not a very efficient solvent. Let me show you the data we generated. There's only 16 percent that was extracted from reformulated OxyContin compared to 13 percent for current OxyContin. This very small 3 percent difference creates a number 123. You can see similar results that generated data 127.

So we can conclude that the small particles release oxycodone faster than larger particles and at the time points tested that's relevant to abusers. As I mentioned, 10 minutes and 60 minutes, the

reformulation released oxycodone significantly slower in all effective solvents tested.

Now let me discuss Study 3. The goal for Study 3 is to assess whether reformulated OxyContin will dose dump in ethanol. This is to simulate a scenario of patients taking tablets together with alcoholic beverage inadvertently. Also, in some cases for abusers, they might also try to take it with alcohol in an effort to get high.

Here is how we approached this study. We used the solution, which is the standard USP basket apparatus, 900 ml, using simulated gastric fluid and/or ethanol in simulated gastric fluid, performing the test at body temperature with constant agitation at 100 rpm. At the end, we generated the amount of oxycodone that can be released at the time points shown here.

Our results indicated reformulated OxyContin does not dose dump in any of the particle sizes we have studied. Similarly, you have no from current OxyContin.

Let me show you the results here. Across

the top is the particle size we studied from small, medium, to large. On the left-hand side showing you all seven strengths of reformulated OxyContin we studied. We used F2 similarity factor to do the data evaluation. F2 similarity factor is a standard statistical methodology that's published by FDA to evaluate the similarity of two dissolution profiles.

Across the particle size, there's no dose dump. It also goes across the strengths. So we can conclude here reformulated OxyContin does not dose dump in alcohol and this holds true across all particle sizes and the strengths.

Now let me discuss Study 5. There are two parts to Study 5. This first part, our goal is to assess whether reformulated OxyContin can be injected using an insulin syringe.

To study if reformulated OxyContin can be abused intravenously, you have to evaluate both syringability and injectability. Here is our approach to conduct the study. For syringability, we look at different temperature, time, and volume of water. We use 27 and 28 gauge needles. Twenty-eight

gauge, as you are aware, is the most commonly used by the abusers because it’s readily available.

We do use 27 gauge in our studies because we conduct our study more than just 2 ml extraction and we need to have a needle that can be attached to a larger syringe. We use a constant drawing up to one minute. At the end we determine the amount of oxycodone that can be syringed and the volume of solution that can be syringed.

Now let me discuss how we approach injectability. In this case, we had to pour the solution in the back of the syringe and then see how much we can expel. Again, we studied different temperatures, time, and volume of water. Here, we used 27 gauge because we need larger volume and water to pour the solution to. You cannot pour into a 28 gauge insulin syringe.

Again, the same constant, expel up to one minute and we determined at the end the amount of oxycodone that can be injected and the volume of the solution that can be injected. Through our study, we have found that reformulated OxyContin cannot be

easily injected or syringed using an insulin type of syringe.

Here, let me show you data for syringability first using a 27 gauge. Showing here is a 2 ml preparation. The number on top is milligram oxycodone. On the left-hand side showing you across the strengths of reformulated OxyContin; to the right showing you the crushed current OxyContin bracket with 10 through 80 milligrams.

As you can see, most of the numbers here are zero, except 40 milligram strengths reformulated OxyContin, a small 2 milligram was syringed. This is because of the excipient for reformulated OxyContin polyethylene oxide hydrogel in small volume. When the hydrogel’s in small volume, oxycodone does not dissolve or extract. Also, the solution that’s produced is very viscous. It cannot be syringed with this preparation with this size of insulin type of syringes.

We wanted to see if we increased the volume, could we potentially get more oxycodone being syringed. So we used ten 5 ml preparation, same set-

up. You can see we get a little more, but still the maximum amount is only 6 milligrams from a 30 milligram reformulated. And compared to current, you get 71 milligrams from an 80 milligram tablet. Even upping the volume to 5 ml, the solution is still viscous.

Now let me show you the results of injectability. Here, as I have discussed, 2 ml is just too thick. You cannot pour. So we used a 5 ml. With injecting through the back of a syringe, we got a little bit more, but worse case still is 40 milligrams from 80 milligram tablet compared to what you can see, 60 out of 80 from current OxyContin.

So reformulated OxyContin really cannot be easily injected or syringed, even with upping the volume to 5 ml.

In order to abuse a product through intravenously, you first have to take an intact tablet. You have to crush it. You have to dissolve the active, and then you can syringe and inject. Current OxyContin is quite easily crushed. Oxycodone can be dissolved and then successfully syringed and

injected. For reformulated OxyContin, it's very difficult to crush and the oxycodone does not dissolve because of the hydrogelling property of polyethylene oxide. And because the resulting solution is viscous, it cannot be syringed or injected using an insulin type of syringe.

Now let me discuss the second part of Study 5. The goal for this study is to simulate smoking of reformulated OxyContin and compare that to known controls that are efficient for smoking.

Here is how we approached this study. First, we had to perform vaporization. We used heating block to hold the constant temperature with constant air flow to simulate inhalation of a smoke, and we collected vaporized oxycodone using a solid face cartridge.

Now for this study, it's very important to determine the proper temperature that can maximize the vaporization and minimize burning. We did a lot of studies in our laboratory to find out what is this optimized temperature and we determined it's a very narrow range. So we did this for reformulated

OxyContin and current OxyContin. We also included in our study two appropriate controls, a negative and a positive, to demonstrate the validity of our procedure. At the end, we determined the amount of oxycodone that can be vaporized.

Through our study, we found both reformulated and current OxyContin cannot be efficiently smoked. Let me show you the data here. On the left-hand side from the top first are the seven strengths of reformulated OxyContin. In the middle here is current OxyContin bracketed with 10 to 80 milligrams, then the two controls I just discussed.

What I also included here are three references. These are the illicit drugs that is known to be abused through smoking. As you see the data on the right-hand side, X is meaning the yield we can vaporize from reformulated OxyContin all the way down to including current OxyContin or low, which is supported by our negative control.

The positive control here is showing 68 percent that demonstrated the validity of our

procedure. And this compared to the three references I just mentioned has very high efficiency from 80 to 98 percent. So we can conclude that our procedure does demonstrate a positive control showing the material can be vaporized. And the current OxyContin, although it can be crushed, it cannot be efficiently vaporized. For reformulated OxyContin, it cannot be easily crushed and also it does not vaporize efficiently.

Now let me summarize the findings from all our studies. Reformulated OxyContin tablets are difficult to crush. They release oxycodone slower than current OxyContin tablets in a range of solvents, even when the tablets are reduced to particles.

They do not dose dump in ethanol, even when reduced to particles. They are difficult to syringe or inject using an insulin type of syringe, and they are inefficient to release oxycodone through vaporization.

Thank you.

DR. LANDAU: Thank you.

Our next speaker will be Dr. Ed Sellers. Dr. Sellers will provide his interpretation of the in vitro program and its results and also provide his views on the potential impact this formulation may have on multiple subpopulations.

DR. SELLERS: Thank you, Craig.

Good morning, everyone. My name is Dr. Ed Sellers. I've been asked by Purdue to provide an independent evaluation of the preclinical studies and to forecast what I think the public health consequences of their change in formulation are likely to be.

First, I'd like to give the committee some background on myself, so you can place my comments in perspective.

I'm a medical graduate of the University of Toronto and have a Ph.D. from Harvard University, and I'm board-certified in Internal Medicine, both in the United States and Canada.

I'm currently a Professor Emeritus at the University of Toronto. For the past almost 40 years I've been deeply engaged in research in clinical care

with respect to therapeutic drugs that have dependence and abuse potential.

My work has covered the full range of preclinical to clinical to post-marketing studies. My colleagues and I have published over 600 peer-reviewed scientific papers and a number of these have been in leading journals, such as *Nature*, the *Journal of Pharmacology and Experimental Therapeutics*, *Clinical Pharmacology and Therapeutics, and Drugs and Alcohol Dependence.* I've frequently been asked to write chapters and reviews.

I'm currently a member of the World Health Organization, Expert Committee on Problems of Drug Dependence. I'm a past president of the American Society of Clinical Pharmacology and Therapeutics, foremost society of clinical pharmacologists, and a past president also of the College of Problems of Drug Dependence, the leading organization that considers issues of abuse liability.

In my past, I was also former vice president and medical director of the Addiction Research Foundation in Toronto, Ontario, a leading

research organization in the field.

At present, I'm Vice President, Kendle International, for their early-stage part of their business. Kendle is one of the world's leading contract research organizations, provides services to the biopharmaceutical industry. Kendle's early-stage unit in Toronto is particularly well known because it is the foremost research center for the conduct of human abuse liability studies and tampering studies, and that group has conducted more than 200 such studies.

Before I continue, I want to tell the committee about my relationship with Purdue and that of Kendle with Purdue.

First, the opinions that I'm going to share with you are entirely my own and based on our research and my understanding of the scientific database that tells us about what abusers do and why they do it.

I'm appearing today as an independent consultant. Kendle will be paid for my time by Purdue Pharma.

In addition to providing services to Purdue, I've worked with virtually all of the other leading pharmaceutical companies to either advise them on drug development issues as related to abuse liability and tampering and in a number of cases have actually performed such studies for them.

I should probably note, give as a footnote, that Kendle was not among the CROs that performed the in vitro testing.

Like Dr. Cone, I've done previous work with Purdue, started in October 2008, where I was a member of an expert panel that advised Purdue on what abusers do and what kind of in vitro testing systems and programs they should implement.

In January of this year, I attended a closed FDA meeting with Purdue where the Purdue approach to in vitro testing was discussed. In February of this year, I reviewed the in vitro data that you've just had presented. And since April 2009, I've been working with Purdue on the development of a number of post-marketing studies.

From this interaction with Purdue and with

many other companies, my evaluation of this in vitro program that's been developed and executed by Purdue is that this program is the largest and most carefully-conducted such program that I've encountered anywhere in the industry. There may be something else out there that's bigger and better, but I haven't seen it yet.

Now, in the course of our research work, we've conducted a number of indepth surveys and interviews with abusers, so we're very familiar about what they like and what they don't like. The Internet in particular is a particularly rich source of information about what abusers are thinking about, what they're going to do, and what they are doing at the moment. And I'd like to share with you some of the kinds of things -- you've seen some of these from Dr. Cone, but I want to share with you a few that are particularly pertinent to the new formulation.

The place to start is perhaps what do abusers say about preparations that gel and contain polyethylene oxide. There is one such product on the market at present. It's methylphenidate. It has a

trade name of Concerta. It's a controlled-release dose form. The drug is used for the treatment of ADHD. It was developed in part to address the problem of the abuse of methylphenidate, which exists in an immediate-release form. And one trade product name you might be familiar with would be Ritalin.

So here's a representative quote. I don't have obviously time to share all this information, but I can assure you that these quotes are exactly what you will see repeated again and again on the Internet.

"Concerta, when crushed up and snorted, has been known to completely clog up the nostrils as it turns into a slime. I wouldn't inject it unless, of course, you want your blood to become the consistency of maple syrup. Concerta is only good for eating, no matter what you do with it." And then there's sort of a little editorial comment from this individual, "and even eating it is pointless."

Now, there are other products out there that have some hydrogelling types of properties and here's another kind of quote. "In terms of

potency," -- and this is relative to oxycodone-containing product, "In terms of potency, they should be no different in any brand. However, some brands are a pain to crush and if you want to sniff them, they turn to gel." So this is kind of an echo of what Dr. Cone was telling you about.

Finally, you've heard some data about vaporization and models of smoking oxycodone, and the first point is that this is not a very common or very successful kind of thing for people to do with the existing product and here's some quote that bears on that.

"I've heard of people smoking OxyContin with success, but I don't get how that works with all the binders and fillers that's in Oxy. I tried it once and it was very disgusting. I didn't feel anything from it. I even tried it with the instant-released oxycodone, and that was just as bad as smoking 40 milligrams of OxyContin."

The reason that it's disgusting to them is that the product contains excipients that when you start to vaporize them, it produces basically a glop

and it's very inefficient. It's very hard to vaporize oxycodone right off. And I would anticipate when you mix it all up with the polyethylene oxide that you're certainly not going to see an increase in this behavior, and I would expect it to be even less smoking.

Now, over the past 15 years, we've learned a lot about tampering, determinants of abuse liability and abuser behavior, and I'd like to review what we have learned.

In the upper two panels of this figure, I've summarized pictorially the observation that has been seen across a wide range of different drugs and different formulations, that the in vitro dissolution pattern matches to what we then find with in vivo kinetics of the drug and so this is kind of a cartoon version of an immediate-release drug and a controlled-release drug and the profiles. You can see the similarity.

The third panel summarizes what we have learned about the relationship of kinetics and liking. And what it shows is that abusers like the

IR type of dose form because they've got greater liking and have greater preference for it. And this is something that happens in the first hour or so when the drug is taken.

If you take a controlled-release dose form and spread out the kinetics, what you find is you get much, much lower kinds of reports of liking and preference. And in fact with some of the controlled-release dose forms, what you find is later, after they've received the drug, they don't like the drug at all; they report disliking it. And that's because a number of the adverse effects start to kick in.

So this is a pattern that we see again and again with different classes of drugs, not only opioids. You see it with stimulants. You see it with a variety of sedatives and so forth.

In the past 15 years, we've learned that abusers will tamper and we've learned that abusers don't like gels. They don't like excipients. They don't like hardness. They don't like additives, and they do a lot of things to avoid them.

They like fast and easily-powdered, and they

like to be able to get it into a solution that is clear. I'm describing basically the currently-marketed formulation of OxyContin. When it gets hard, they go looking for something that's easier. So they will gravitate to use immediate-release dose forms or other drugs that are more easily tampered with.

Now, based on what we've learned about abuser behavior over the last while, I think we can be pretty confident that we can anticipate that the changes in formulation are going to move the safety and the public health implications sort of in the positive direction.

Now, what we can't predict is exactly how far this positive change is going to occur. Now, in that context, Purdue asked me if they should do in vivo studies, liking studies or something of that sort, in order to bring greater certainty to the prediction about the direction and the size of the change that one would expect with this formulation. And it was my opinion that for an approved product, for which there was a recognized public health

problem, that yes, you'd generate more data, but you actually wouldn't be able to predict any more precisely the size of the change. And, therefore, I advised them that they wouldn't learn anything that would give them any greater precision or anybody else. And I think you've already heard that there are going to have to be epidemiologic studies to answer that question precisely.

But from the data at hand, I think that the direction of change is clear. What's at debate is, is this a 20, 30, 40, 50, 60, 80 percent improvement? We can't answer that quite yet.

Now, when a controlled-release dose form is prepared, the first thing is you're obviously directing it at patients for benefit. There's no point in producing a dose form that doesn't release drug. So you're balancing the benefit to the patient against safety and risk. That's for the intended population.

Then there's some issues with non-patients, people who abuse. And then there are some conditions of use that you never intended but you have to be

concerned about, and you've heard a number of the attempts that Purdue has made to try and understand some of those unusual kinds of behaviors.

So let me tell you what I think is the implication of the in vitro testing you've heard about with respect to patients. With patients, of course, we have examples of them accidentally or intentionally modifying the existing formulation by crushing it between two spoons. It's trivial to do this, and then it can be sprinkled, and things that were never intended could be done. And this has resulted in misadventure, and I think it's clear that patients and caregivers are not particularly motivated to go and do this. And so I would categorize what goes on now as sort of accidental or misadventure. I think that it's quite clear that the new formulation is going to change that.

The next group to consider, I guess, would be the non-patient group. So these are the abusers, and you've heard several times that the harder the tablet is, the less likely is that tampering is going to occur. If it's more difficult to crush or

dissolve, it’s less likely that it’s going to be abused.

I think because of the gelling properties of this product, whether it’s something you’re thinking about injecting or putting in your nose, the gelling properties are going to be a pretty big deterrent to those behaviors.

Now, there is one situation which has already been alluded to, and that is there is some abuse of the intact existing formulation of OxyContin not particularly common, and hard-core abusers tamper with it. So some people do take the controlled-release because of a long-term kind of effect. Obviously this new formulation is not going to do anything about that. That will be basically an enduring issue with all controlled-release tamper-resistant-like products.

So let me now summarize, using the kind of template that you’ve seen before, what I think is going to happen wit respect to safety and public health advantage.

First of all, I already mentioned that

there's going to be no impact of the new formulation on the abuse of the intact product, but I think that we can be pretty confident that there will be a directional positive change with respect to crushing, crushing and extracting, nasal crushing and snorting, rectal use of the drug. Smoking might not be too big an effect there; injection, crushing, extracting, and so forth, again, I think we'll see that will be an improvement. And then I've already mentioned that I think for patients, that there's not going to be any casual or accidental kind of crushing occurring. This tablet is simply just too hard for that.

Finally, I suppose we should look at sort of populations of people who we might regard at risk and look at what might happen to the safety profile there. There are some situations of accidental misuse. I suppose one example would be maybe a child that got ahold of prescription drugs that weren't under proper control by the person who had the prescription. And here, you know, it's very easy for a child to disrupt the existing formulation because it's very, very soft, and that kind of conversion of

a potentially high-dose-containing dose unit into an IR form could be lethal.

So I think that that will be much, much improved.

There's another group of individuals who are kind of a composite of experimenters, opportunistic use, peer-driven use, incidental use at a party. I think again here, they're going to see fewer problems than have been already recognized with the existing formulation.

With recreational abusers, that would be individuals who are using more consistently, I think what you'll see here is that they're a group that generally don't want to put much work into finding a drug to abuse and you'll see them either stopping, reducing, or they're going to gravitate to use some other immediate-release dose form.

The final group, I suppose, would be the sophisticated or hard-core kind of addicts. There are a few of these individuals who take pride in being able to defeat any technology. They consider it to be an intellectual game, but, of course, there are very few of them. This group will also shift

their patterns of use, and I think what you'll see is that, again, there will be a positive impact on this group, but it's going to be the more resistant group. But remember, when we think about abusers, the vast majority of them, at least 70 percent, are not in this kind of hard-core group, and so they're a group that are going to be -- you know, the vast majority are going to be affected by this new formulation.

So in conclusion, I guess I'd share with you that abusers prefer immediate-release dose forms. Eighty percent of abuse of opiates is already with immediate-release dose forms or dose forms that are easily converted to IR. I think that the new formulation is better from a patient and a public health point of view. The in vitro studies you've heard about are the most comprehensive I'm aware of, and it is my opinion that if this new formulation is approved, that it should have a positive public health impact.

Thank you for your attention.

DR. LANDAU: So I'd like to conclude with a few remarks on what we know about the reformulation.

We presented earlier data demonstrating the fact that it's bioequivalent to the current product, and on this basis should be considered therapeutically equivalent for the million or more patients each year treated with it to manage their pain and maintain a quality of life.

Based on its physical-chemical properties demonstrated through the in vitro program, it's an important advancement from a formulation perspective. It'll be more difficult to prepare for abuse via multiple routes, and on the patient side, it'll make it less likely that patients will be exposed to oxycodone through inadvertent chewing or intentionally through an otherwise well-intended caregiver.

It's our intention, if approved, to introduce all strengths of the new reformulated product simultaneously and transition to this new formulation just as soon as we can.

Thank you. This concludes our presentation, Mr. Chairman.

DR. KIRSCH: Thank you. Thanks to all the

speakers on behalf of the sponsor.

We will now take a break for lunch. We will reconvene in this room one hour from now, which will be at 12:45 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any members of the audience. Thank you.

(Whereupon, at 11:44 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. KIRSCH: Welcome, everybody, back from lunch. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual’s presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your

written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor’s payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be

conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

For the speakers, there will be a green light on when you begin to speak. It will turn yellow when you're near the end, and then it will turn red. After your time allotted, the speaker will turn off and we'll ask you to step aside. Thank you.

So the first speaker that's recognized is Mary Bennett.

MS. BENNETT: In terms of your request, I have no financial disclosures.

My name is Mary Bennett, the Director of Grassroots Advocacy for the American Pain Foundation, which is a non-profit organization whose mission is to improve the quality of life for people with pain by raising public awareness, providing practical information, and advocating to remove barriers, increase access to effective pain management.

Pain affects more than 76.5 million Americans. It is the number one reason people seek medical attention. There are more Americans affected by pain than cancer, diabetes, and heart disease combined.

Whether pain is a result of a disease, a car accident, or injury sustained in combat, the lack of pain care can make life a living hell. Some have described their pain as a form of torture.

The lack of access to effective treatments has a tremendous impact on every part of one's life and can rob a person of dignity, the ability to function, the capacity to contribute to one's family. The under-treatment of pain costs approximately $100 billion annually.

We recognize the need for a broad range of pain treatment options. Opioid analgesics, when taken as directed, have effectively provided life-saving relief for millions of Americans with moderate to severe pain. Do not abandon those who benefit from round-the-clock, long-acting opioids and the new abuse deterrent.

We share your commitment to protect public health. We recognize the serious problem of prescription drug abuse and illegal use and the need for strong and effective measures.

A fundamental question is should illegal and criminal activity dictate the care for others? Should people with pain who are using medications as directed be victimized by illegal use and accidental overdose?

It is critically important to aggressively address prescription drug abuse and its tragic impact with effective strategies but not at the expense of millions of people with persistent pain. Policies and public health strategies that curb drug abuse without undermining relief for patients in pain are possible and are in the best interests of society.

The development and approval of extended-release opioid medicines, which are intended to reduce the risk of abuse and diversion, is a welcomed advance. Many people living with pain do not have access to these medicines because far too many healthcare providers fear that these medicines might

get into the wrong hands.

DR. KIRSCH: Thank you.

MS. BENNETT: Thank you very much.

DR. KIRSCH: The next speaker will be Don Bivins.

DR. BIVINS: Thank you, sir. I have no financial disclosures to make.

I am Dr. Don Bivins, and I am a patient. My career was interrupted in 2006 when I developed pain and weakness in both legs. I did not have pain control because the physicians prescribed short-acting opiates. I had to lie on my stomach 24 hours every day because the pain was terrible. I slept less than three hours each day.

Four months into my illness, I achieved significant pain relief because long-acting opiates were initiated. I then could feed myself but required assistance for dressing. Five months into the illness, the doses of the long-acting opiates were adjusted and I could walk into other rooms and begin to dress myself.

I am also a physician, having practiced or

taught pain management from 2001 until the present. I live and work in Southwestern Virginia, an area well known for the misuse of prescription pain medications.

A colleague of mine researched many deaths related to OxyContin misuse in Southwest Virginia. The demographics separated into two groups. The largest group was depressed middle-aged women on multiple medications from multiple physicians and who died of accidental overdose. The second largest category was young people who used a variety of prescription drugs with alcohol and marijuana. They unknowingly but dangerously mixed these street drugs and prescription analgesics. They also died of accidental overdose.

When I had an active clinical practice, using long-acting opiates was a necessity for more than 50 percent of my patients. Long-acting pain medicines allowed patients to return to work or to gain independence in activities of daily living. Several of my patients were able to leave retirement and medical disability to return to gainful

employment.

I am well aware of the usefulness and the difficulty associated with long-acting opiates. There is a potential danger in using the long-acting opiates. It must be emphasized, however, that the danger occurs when the drugs are misused or prescribed incorrectly.

I sincerely regret that families have lost a loved one to the misuse of these medicines. Making the drugs more difficult to misuse is the logical next step. The appropriate training of healthcare providers is vital.

I commend Purdue for the new formulation and urge this committee to expedite its approval. Your approval will protect patients with legitimate pain disorders and will protect families whose children or siblings misuse long-acting opiates out of ignorance or out of innocence.

Thank you.

DR. KIRSCH: Thank you.

The next speaker is Dr. Gregory Bogdan.

DR. BOGDAN: I'll disclose that Purdue

Pharma is a subscriber to the RADAR System.

Good afternoon. My name is Greg Bogdan, and I am the Research Director for the RADAR System, which is owned and operated independently by the Denver Health and Hospital Authority. I'll be presenting on the RADAR system and its ability to evaluate changes in prescription drug abuse, especially as it may relate to the reformulation of OxyContin.

The strategy behind the RADAR System is simple: to provide multiple perspectives on the misuse, abuse, and diversion of prescription medications.

The RADAR System provides that perspective from six signal detection systems representing the criminal justice system, treatment professionals, acute health events caused by abuse, the perspective of patients under treatment, impaired nurses, pharmacists, and physicians, and college students.

These six signal detection systems identified a specific product and formulation that is being misused, abused, and diverted, coded to a

three-digit zip code. This gives us the ability to address every part of the pathway of addiction from initial experimentation to relapse after remission.

What the RADAR System may see after the introduction of a reformulated OxyContin is that the reduced rates could either stay the same, increase, or decrease, and this would be compared to abuse rates for other oxycodone and opioid drugs. No matter what the outcome, we would have the ability to monitor changes in abuse rates. Previously the RADAR System has shown the ability to detect changes after a community intervention.

I'm going to talk to you now about Kentucky UNITE. Kentucky UNITE's first activities were initiated in 2004 in a 29-county region of Eastern Kentucky. These interventions included but were not limited to undercover narcotics investigations, 800 numbers for substance abuse and treatment support for family members and friends, and education efforts.

Using RADAR System Poison Center data, one of our six systems, the three-digit zip codes in Kentucky were classified into the Eastern or UNITE

region and then the Central Western region.

Average regional intentional exposure rates per 1,000 unique recipients of dispensed drug were calculated for all oxycodone drugs, as depicted on that slide there.

Our data indicated that the intentional exposure calls were more common in the UNITE region than the Central Western region before the initiation of Kentucky UNITE. Rates for oxycodone drugs then decreased after implementation while they seemed to increase in the other part of the state. Recently, the rates are starting to go up again. It will be interesting to see what effect a reformulated OxyContin will have on these trends.

In conclusion, OxyContin's reformulation offers a great opportunity to evaluate the impact on prescription drug abuse, misuse, and diversion. There are many perspectives to drug abuse and each represents a different population. And the RADAR System can provide data related to these different perspectives and has experience in evaluating interventions.

Thank you for your time.

DR. KIRSCH: Thank you.

The next speaker is Jennifer Bolen.

Is Ms. Bolen here?

[No response.]

DR. KIRSCH: Okay. We'll go to the next one. Fred Wells Brasen.

MR. BRASEN: Good afternoon. I represent Wilkes County, North Carolina. I'm Project Director for our Chronic Pain Initiative as well as chairing the Substance Abuse Task Force for Wilkes County and the Western North Carolina Region.

In that, we're the first county and actually the first state to begin a naloxone-dispensing program called Project Lazarus in order to hopefully stem the overdoses that are occurring in our region of North Carolina. And I do have to state I'm here at my own expense. There's no financial disclosure regarding what I'm sharing.

In Western North Carolina, the average death rate per 100,000 from opiate drugs is 16. Wilkes County, it's 41. The state average is 11, and

in the United States, it's about between eight and nine per 100,000.

So we took a community coalition approach. We took the rescue medication approach. We took a physician education approach, CMEs, on proper prescribing. So we've looked at the whole scope.

Another responsibility that I've had is director of our local hospice and I'm also the hospice chaplain. So I've been working on both ends, working with the individual who was abusing or misusing and dying from the opiate drugs, and then I've also been working with those patients, those pain patients who desperately need the opiate narcotic in order to have a comfortable functional lifestyle.

So in saying that, such a formulation as this to make it safer, less abusable, I have to say we want that in the individual's -- well, not medicine cabinet. We have to say lockbox because that's preferred because of the stealing that's going on. But in so doing, we have to look at the whole community aspect regarding opiate-prescribing.

The community needs greater and more education because the abuser is going to do what they feel that they need to do to try and get the drugs, so we have doctor-shopping. We're addressing that with law enforcement. But then the other side of that is we're educating the abusing population and we're educating the misusing population, because the abuser needs to know that if they do this to this medication, crush it, snort it, inject it, they are at greater risk because they've changed the dynamics of the drug.

So if the pharmaceutical companies, such as Purdue Pharma, is changing the formulation to make it where that does not work, does not meet the abuser's intent, then we have stepped into that arena of the community that needs to be addressed and making it safer, because, as I work with chronic pain patients every single week, I head up a support group, they need the medication in order to function, and we can't -- you know, just because somebody speeds in their vehicle doesn't mean that all of us have to lose our cars.

So it’s the same thing with the abuser. Just because somebody is doing something illegal, we can’t take it away from the individual that needs that narcotic prescription. So we are working with the physicians, and I encourage you and the other pharmaceutical companies to do the formulations that are necessary to make it safe because I’ve got 41 people in my county who died last year.

Some of those were abusers, some of those were misusers. And it’s probably right now about the number one county in the United States, and I thank you for your time and appreciate it.

DR. KIRSCH: Thank you.

The next speaker is Maggie Buckley.

MS. BUCKLEY: Thank you. I have no financial disclosure.

My name is Maggie Buckley. I’m a wife, daughter, sister, friend, aunt, neighbor, and photographer. I live with Ehler-Danlos Syndrome or EDS, a painful genetic connective tissue disorder that causes joint dislocations and excessive bruising.

Living with EDS is like trying to move through the world during an earthquake, never knowing if the next footstep will land flat on the floor or if I will fall and dislocate something else. Pain has been my constant companion since childhood. The pain levels range from mild to so excruciating I find myself unable to form words, let alone speak.

I'm here today to discuss why long-acting opioids are as important a part of my pain management arsenal as my assistive devices. Long-acting opioids are just one of many tools that I use to manage my pain. Though I don't use all of them all the time, I do use them for extended periods of time as part of a recovery process from the frequent dislocations and injuries.

Each tool is a key to my overall health. When there's a spike in pain or injury levels, the controlled-release medications have been the best intervention to get me back on track.

I've been prescribed these types of medications successfully at different points in my life for varying lengths of time. I have lived

without long-acting pain medications but that life left me looking for a way out and feeling that I was a burden to others.

In my teens, I was prescribed NSAIDs, which left me with GI irritation. In my twenties, exercise and working through the pain were recommended in spite of poor muscle tone due to EDS and an increase in injuries from the increase in exercise. In my thirties, I was lucky if a short-acting opioid was offered.

Eleven years ago, I suffered a horrendous hip dislocation and was forced to leave the workforce for rehabilitation and recovery. Rest, ice, heat, physical therapy, short-acting opioids, anti-nausea medications and laxatives were the only tools available to me. I would get a little better, push a little harder, and then injure something else.

By 2000, I had reconciled myself to being depressed and dependent upon others. I primarily used a power wheelchair to get around. Some days I couldn’t get out of bed or even eat because the pain was so bad. Emotionally, I felt defeated and I felt

like dying.

The cycle of untreated pain, depression, re-injury and hoping for a lifeline continued until 2003 when a physician prescribed a long-acting opioid after I had concurrent shoulder and ankle dislocations. I felt like I was freed from prison. Taking the prescription as directed for a period of three months allowed me to fully participate in my own care, actively exercise, enjoy the company of friends and family, and be engaged fully in my own treatment plan.

The nature of the long-acting pain medication minimized the wild fluctuations in my pain levels that had previously prevented me from living my life. Long-acting opioid medication has saved my life. This medication choice has come to my rescue more than once, and I hope it will be there again when I need it as I continue to live with EDS and the pain it exerts on me. The responsible use of long-acting opioids makes it possible for me to recover.

DR. KIRSCH: Thank you.

Our next speaker is John Carney.

MR. CARNEY: Thank you. I'm John Carney from the Center for Practical Bioethics.

The center has, during its 25-year history, received at times unrestricted gifts from the sponsor, as from a number of other pharmaceutical companies, to improve access to quality end-of-life care.

We owe a particular obligation to those who are traditionally underserved, including some of our most vulnerable patients, our long-term care residents, and those living in nursing homes and others, including those of ethnicities and disenfranchised populations.

New American Geriatric Society guidelines call for the treatment of pain, for chronic pain for elderly people, to be opioids as opposed to NSAIDs. And placing additional scrutiny in this already over-conservative area of long-term care poses significant risks for those patients and a return to the world of the 1980s in which baby aspirins were really all that was dispensed in long-term care settings for chronic pain.

The principle of respect for autonomy is a fundamental tenet of healthcare. The Center for Practical Bioethics has for more than 15 years worked with the National Associations of Attorneys General, the Federation of State Medical Boards, the DEA, and pain policy advocates from across the country in developing balanced pain policy strategies familiar to many in this room.

Dignity is an essential component of personhood. Informing and maintaining a sense of who we are, we become self-directed. When you are robbed of the ability to be self-directing, our dignity and personhood is jeopardized. When that loss of sense of self is preventable and treatable, as it is with pain, healthcare providers have an obligation to act.

Pain steals from its victims and punishes them unnecessarily and our collective professional responsibility to protect those persons is something that cannot be restricted. We must remember above all else that pain is subjective.

Our under-treatment should be subject to as much scrutiny as our concern for the legitimate risks

associated with misappropriation, and the principle of justice cannot be subjected to over-simplification.

Do we treat pain the same or do we treat people according to their need? When the consequences are minor and the inconvenience is a nuisance, then all can be asked to make adjustments. However, the pain patients require more from us because of the price that they have to pay because then they become victims twice over, once because of their health condition and once because they need treatment and seek drugs.

There is no question that what we need is a balanced policy and thoughtful consideration and restraint and dutiful attention for both the policy formulation and the treatment that patients need.

The preponderance of literature in this area deals with misappropriation and treating patients as addicts and subversive activities. These characterizations get amplified when policies get implemented, especially in relation to race, ethnicity, and cultural language barriers.

The ominous tone will only grow more dark if we are not vigilant and work to implement balanced pain policy.

Thank you.

DR. KIRSCH: Thank you.

The next speaker is Charles Cichon.

MR. CICHON: Good afternoon. I'm Charlie Cichon. I'm the Executive Director of the National Association of Drug Diversion Investigators.

DR. KIRSCH: Sorry.

MR. CICHON: That's fine. Nobody ever gets it right. NADDI.

I have nothing to declare, but I will discuss some sponsorships and unrestricted grants that NADDI has received from Purdue Pharma, as well as other pharmaceutical companies.

NADDI is a non-profit organization dedicated to providing education to its members and the public on the issues surrounding prescription drug abuse and diversion. The majority of our members are law enforcement, but also included is a considerable population of regulatory agents,

healthcare professionals, and healthcare fraud investigators.

Due to the ongoing problems with drug diversion in the United States, NADDI is a strong proponent of new controlled substances that make it more difficult for an abuser and more helpful for law enforcement, yet still provide quality relief to the patient.

NADDI has a strong belief that the diversion of prescription medication can many times ultimately negatively affect legitimate patients, the vast majority of those who use controlled substances.

NADDI has provided grants to law enforcement agencies across the country, most recently to the Kentucky Office of the Attorney General, Drug Diversion Task Force, a statewide task force originally formed to focus on stopping prescription drug abuse and diversion in Eastern Kentucky.

NADDI’s Seed grant is sponsored by Abbott Labs and is designed to encourage local and state law enforcement to dedicate at least one full-time law

enforcement officer to investigate prescription drug abuse.

Sponsorship by Purdue Pharma supports our Abused Pharmaceutical Substance Brochure. This brochure is designed to be a field reference for law enforcement officers across the country. NADDI has dispensed over 400,000 of these brochures free to law enforcement officers throughout the United States.

NADDI's law enforcement grant was developed through sponsorship provided by Purdue Pharma to help address the complex problem of prescription abuse and diversion and put more resources in the hands of local law enforcement entities engaged in combating the abuse and diversion of scheduled prescription drugs. The LE Grant Program is designed to recognize law enforcement agencies that have achieved excellence in the investigation of pharmaceutical diversion.

NADDI's 20th anniversary conference in November is in Annapolis, Maryland, and one of the highlights of that conference will be a program entitled Teens in Crisis. This session will involve

a group of teenagers that have had a severe addiction to prescription drugs and are traveling around the country to tell their story. The Teens in Crisis presentation is sponsored by King Pharmaceuticals.

Purdue Pharma is a leader in the industry with its collaborative efforts with the public and law enforcement and here are several examples. Painfully Obvious is a public service campaign designed to educate parents, teachers, and students about the dangers of prescription drugs. Prior to Painfully Obvious, there was no national program to address the growing issue of prescription drug abuse among young people.

DR. KIRSCH: Thank you.

MR. CICHON: Thank you very much for your time and attention.

DR. KIRSCH: Thank you.

Next is Michael Clark.

DR. CLARK: Good afternoon. I'm Dr. Michael Clark. I have no financial disclosures.

I'm a psychiatrist, pain specialist, and member of the Board of Directors of the American

Society of Pain Educators. This is the only organization in the United States focused solely on pain education. We have been actively involved in the risk evaluation and mitigation strategies hearings, writing to the docket with regard to REMS and acetaminophen.

We well understand that effective education is the best approach for improving treatment adherence and compliance, assuring safe use and helping patients to raise their function and quality of life.

Today, on behalf of the American Society of Pain Educators, I come to support continued access to controlled-release opioid analgesics. These vital medications are life-affirming for people with around-the-clock moderate to severe pain. They afford continuous pain relief and stabilize blood levels to minimize side effects and enhance their established efficacy.

Consistent with the ASPE's previous statements, we believe that access to controlled-release opioids, such as OxyContin, is necessary to

maintain excellence in pain management for legitimate patients.

We support any and all efforts made to make these medications resistant to tampering by people who would misuse them. We recognize that there may never be 100 percent tamper-proof medications because such forms would likely not relieve pain. However, we do believe that efforts to minimize conversion from controlled-release to immediate-release by matrix destruction will improve the safety of these medications and lessen their desirability for purposes of recreational use or intoxication.

The ASPE respectfully calls upon the members of this advisory board to answer the questions posed by the FDA. Today's meeting is about a formulation change for a single medication. It is not the time nor appropriate forum to address all of the concerns related to REMS or other product technologies.

OxyContin has been an effective medication, able to help those with chronic disabling pain live more satisfying lives. We ask that you review the

data with proper deliberation and allow practitioners to prescribe OxyContin in the new and safer formulation.

Thank you for your attention to these important issues and the opportunity to speak to you today.

DR. KIRSCH: Thank you.

Next is Eliot Cole.

Is Dr. Cole here?

[No response.]

DR. KIRSCH: No. Then we'll go on to the next one then. Penny Cowan.

MS. COWAN: Cowan. Thank you.

My name is Penny Cowan. I'm the Founder and Executive Director for the American Chronic Pain Association, and I have nothing to declare. I've no financial obligations.

For almost 30 years, the American Chronic Pain Association has daily contact through phone support, e-mails and our support groups across the country with real people living with real pain. Many of these people use strong medications to enable them

to live a productive near-normal life.

People with pain did not ask for the pain, they did nothing to deserve it, and they would gladly trade it in for a life as it was before it began. However, they cannot. They must depend on their healthcare providers to help them manage a life filled with pain and with fear.

While we understand that safety is the number one concern, access to care and personal dignity must be preserved while helping to establish a clear understanding of the risks and safety issues.

People with pain fear increasing the stigma already attached to the use of opioids. Establishing a national registry for those who need opioids to function violates the HIPAA and personal privacy. We all know that there’s little these days that is safe from intrusion, be it cyber crime or other means.

Entering every person who takes pain medications into a registry can threaten their employment, insurance, and access to future care. There is no evidence that a registry would reduce the intentional abuse and diversion of these medications.

It only makes life more difficult for the person with pain.

Education is the heart of the appropriate prescribing, dispensing, taking, storing, and disposal of all opioids. This is an issue of both healthcare providers and consumers. Ideally, every healthcare provider should understand pain and have the knowledge and skill to help their patients manage their pain.

Reality is most do not have the training nor would they be willing to obtain it.

A system that requires physicians to register would result in severely-limited access to care for people with pain. To avoid this, certification of prescribers and dispensers should be tied to the existing DEA registration process. In addition, limiting where opioids are dispensed would be of great harm to those living with pain in rural areas and inner cities.

Creating such obstacles for people with pain will not deter those who misuse opioids intentionally. It will only further stigmatize and

punish people with pain who obtain the medications legitimately and who need them to function more fully. Limiting access to care and treating people with pain like criminals does not really address the drug problem facing the nation today.

Thank you very much.

DR. KIRSCH: Thank you.

Our next speaker is Lennie Duensing.

MS. DUENSING: Right.

DR. KIRSCH: Got one right.

MS. DUENSING: Very unusual.

Well, my name is Lennie Duensing, and I'm the Director of the American Academy of Pain Management. We're the nation's largest professional organization serving clinicians who treat people with pain, and we're the only organization that educates clinicians about pain from an integrative perspective. This means that we support a model of care that is patient-centered and brings together all appropriate therapeutic approaches to reduce pain and achieve optimal health and healing.

The Academy recognizes, however, that for

millions of people with persistent pain, this comprehensive treatment absolutely must include opioid analgesics because they remain one of the most effective treatment options for relieving both cancer and non-cancer pain, restoring function, and restoring life.

For those suffering with pain around the clock, the advent of extended-release opioids has brought relief for millions and they've been used safely and effectively and in a variety of treatment settings. But just how extensive is the pain problem?

Consider this astounding fact. There are approximately 33 million Americans who have lived with moderate to severe pain for more than one year. Think about it. If they all lived in one state, and let's call that the state of pain, it would be the second largest state in population in the country, second only to California and larger than Texas.

If the state of pain were a reality, there'd be two U.S. senators and over 30 members of the House of Representatives speaking out with

passion to guarantee that these long-acting opioids be made readily available to their constituents.

I have another fact. There are approximately 4 million Americans who are using long-acting opioids to relieve their pain. This is over five times the population of the District of Columbia. So think about that while you're driving home tonight.

But what does it mean to live with pain? We know that persistent pain robs people of their lives, of their families, of their work, and even simple pleasures. And we know that pain also robs people of their bodies. And I'm not going to go through all of the various ways, except to let you know that a study came out this last week that showed that the physical abilities of people who had ongoing pain who were 50 to 59 were comparable to people who were 80 to 89 who did not have pain.

Over the last 12 years, working both with the American Pain Foundation and the Academy, I've taken many suicide calls, too many suicide calls, from people who said that they could not live another

moment.

Just this last month at the Academy, we heard from a woman who said that her husband had his pain medications reduced because his doctor was afraid of prescribing. His pain became unbearable and he shot himself in the head.

You at the FDA have been charged with the task of ensuring that the benefits of these drugs continue to outweigh the risks. On March 3rd, Dr. Rappaport said, “We expect companies marketing these products to work with us to get this done expeditiously.”

DR. KIRSCH: Thank you.

The next speaker is Lisa Fowler.

DR. FOWLER: I have no financial disclosure.

Good afternoon, and thank you for the opportunity to share a community pharmacy perspective on the approval of a long-acting opioid medication.

I am Lisa Fowler, Director of Management and Professional Affairs at the National Community Pharmacists Association. NCPA represents America’s

community pharmacists, including the owners of more than 23,000 community pharmacies, pharmacy franchises, and chains. These stores dispense nearly half of the nation's retail prescription medications.

I am a pharmacist, and up until just about a year ago, I spent my days behind the counter of one of NCPA's member pharmacies. I know that OxyContin and medications like it, when used as indicated, ease the suffering in the lives of patients with prolonged moderate to severe and chronic pain.

It is important to note that in the provision of care process, pharmacists have standard workflow procedures that ensure prescription medications are delivered safely to their patients. Face to face counseling with the pharmacist at point of dispensing reinforces proper medication use and detects non-compliance, which can be immediately addressed.

Related to activity at FDA regarding class-wide REMS for long-acting opioid products, NCPA asserts that an automated standardized REMS process that can be integrated within existing pharmacy

workflow is critical to the successful execution of the program.

I also want to stress that community pharmacies are highly regulated in each state by boards of pharmacy, in addition to being regulated by the DEA. It is therefore NCPA's position that any state and DEA-licensed pharmacy should be eligible to dispense opioid products.

Finally, NCPA supports regulation changes that will allow for a simpler take-back process of controlled substances. Typically, patients must wait for a take-back event that is staffed with law enforcement and are allowed only to return products which were prescribed to them.

NCPA supports NCPA efforts to encourage disposal of expired and unwanted medications through appropriately-designed drug take-back programs. When there are fewer unwanted doses of controlled substances in the kitchen cupboards and medicine cabinets of our neighbors and relatives, there will be fewer diverted and abused prescription drugs.

Thank you for your time.

DR. KIRSCH: Thank you.

The next speaker is Larry Golbom.

MR. GOLBOM: Does this -- can I move this forward to the first slide?

DR. KIRSCH: One second. It’s loading.

MR. GOLBOM: While you’re doing that, I’m Larry Golbom. Okay.

Can all the committee members please see that slide?

I am Larry Golbom, and I do a local radio show in the Tampa Bay market of Florida called The Prescription Addiction Radio Show, Breaking the Silence.

For those who have missed the past meetings, this first slide is another reminder of why Purdue is here today. For Purdue, it’s all about narcotics distribution and Purdue has ingeniously repackaged and marketed the opium plant to become a major drug cartel in our country. The media and the American public are beginning to understand the opium epidemic that Purdue has started.

You know, America is here with us today.

The petition to ban OxyContin is growing every day. The thousands who have signed the petition and the comments in the handout before you reflect a dramatic difference. Excuse me. I couldn't get that handout to you, but please do ask for it.

There's a reality of death and addiction in every community in America because of OxyContin. Thousands continue to die with OxyContin in their bodies.

The petition has grown by word of mouth. There's no telling how large this movement is going to become. Bracelets are printed. College students are getting involved. Parents and families are uniting.

You know, heroin was on the market for 14 years. We wait for the FDA to make the decision to pull OxyContin. Why does the most dangerous drug in history since heroin continue to remain on the market?

In my hand is the formulation. It can be gotten off the Internet. Dr. Jenkins, Dr. Rappaport, did Mr. Stewart or Mr. Landau tell you that this

product can probably be put in the oven to separate out the active ingredient?

The formulation before you is a product that is probably more dangerous, more dangerous than your original OxyContin, just by simply putting it in the oven.

Dr. Stewart and Dr. Landau, did you tell the committee members that few, if any, heating studies have been done on this product? Which member is going to vote for this product knowing that putting it in the oven may make it more dangerous than the original formulation?

I didn't hear Dr. Cone mention the oven when he gave his presentation. Smoking it could be more deadly, more deadly, than the original OxyContin.

Purdue has continually misled America. I hope today we find out who is running the FDA: a drug company that continually brings embarrassment to the thousands of employees who are dedicated to the FDA or a privately-held legal drug cartel.

After thousands of deaths attached to

OxyContin, I ask the Advisory Committee to help bring sense to the OxyContin fiasco. Recently, we lost a 10-year-old child to this drug swallowing it whole. I hope you're outraged by this news that you can possibly put this product in an oven or smoke it and bring more death to our communities.

Thank you for your time.

DR. KIRSCH: Thank you.

The next speaker is Steve Hayes.

MR. HAYES: Hi. I have no financial disclosure to make to you, except that I paid my own way, as we've been doing, because I'm the director of a medical detox center. I get to treat and try to help the people that this drug company has mostly sent to us because many of the people that come to us are taking OxyContin.

Now one of the things that I was really excited about when I heard that they were going to have a tamper-proof formulation was that they were going to do what they told the FDA, in fact their convicted felon medical director told the FDA in 2002, which was in a few years in a press release

they were going to be making OxyContin with naloxone.

Now I can tell you that addicts and people that abuse it are scared to death of suboxone because of the additive of naloxone.

Did they do that? No. They didn't make an effective blocker. They made something that made it more difficult, but you're going to have a situation where you're being asked to trust a company that Judge Stein said so misrepresented their patent that he was going to invalidate it, a company that in 2007 pled guilty to a felony of lying.

How do you know that their representatives aren't going to spread the word to everybody this is tamper-proof? Oh, the label doesn't say it, but it's tamper-proof because this is what they have done before.

Basically, I think there's another unintended consequence for many of the public that I deal with. That unintended consequence is you are going to have people who are addicts, who are first-time users, who are going to take this pill. And they're going to be told, this new formulation,

you're going to get a buzz. They don't feel anything, so they take another one. They don't feel anything, they take another one, and pretty soon you've got a situation, particularly with more opioid-naïve people, you've got an overdose.

So you've got an unintended consequence of this drug and you've got a situation where what you're being asked to do is put a drug on the market that will be marketed, I guarantee you, as tamper-resistant no matter what you say on the label.

Is it time to do this? Is it time for more people to die because they take this drug? I'm one of the co-sponsors of the Ban OxyContin Petition. I believe this is a drug that should have been off the market. This is a company, except for a miscarriage of justice in 2007, should have been banned from dealing with the government and should have been banned from dealing with the FDA.

So as far as I am saying to you is take a good look because every one of those kids that I find out about that overdosed is going to be on your conscience.

I deal with people dying. It's not myth to me.

Thank you very much.

DR. KIRSCH: Thank you.

MS. HAYES: Hi. My name is Paula Hayes. I'm here representing Sandra Kresser who was going to be here from Salt Lake City, Utah, today, in memory of her son Josh who passed away three years ago next week from a lethal combination of prescription drugs.

These drugs were all prescribed to him by a doctor who knew his complete history of opiate addiction, multiple overdoses, relapses, and rehab treatment episodes, but chose to ignore all of this and prescribe it to him anyway. None of the levels were toxic, but it was the combination of these prescribed drugs taken as directed that killed her son.

During the last two and a half years of Josh's life, he suffered and was held captive by a very dangerous addiction to prescription drugs. Josh's plunge into opiate addiction began on April 13th, 2004, when his doctor first prescribed OxyContin to him for two herniated disks in his back

that he sustained in a work-related injury. OxyContin grabbed hold of Josh by the throat and wouldn't let him go, no matter how hard he tried.

Josh spent over 404 days in active treatment, trying to break the change of this very powerful addiction that was fueled by his back pain, by clueless doctors on addiction who continued prescribing the opiates to him, and by the lies and deceit of Purdue Pharma and OxyContin.

Josh had the love and support of his family and friends. And each time he completed the treatment program, they became cautiously optimistic that he was finally going to get his miracle and go on to live a long, healthy, happy, and drug-free life. This miracle was unfortunately not to be.

Many would have you believe that those who have become addicted and tragically died were to blame for choosing to misuse or abuse these powerful narcotics. I assure you that no one would ever choose to become an addict. The life of an addict is one of untold pain and suffering.

"The only thing my son chose was to seek

help from a doctor that he trusted." This doctor believed the lies that he was told by the Purdue reps about the safety of OxyContin and prescribed it to her son. Both were dead wrong.

Everyone who has become addicted or tragically died from OxyContin are the real victims. It doesn't matter if they were patients with legitimate pain taking it as prescribed, patients who, like her son, became addicted after being prescribed it for a legitimate injury, those who used it for non-medical reasons or those who naively tried it only once, the results are the same: addiction and death. All of those people are the real victims of OxyContin.

We are here today for the proposed approval of a new formulation of OxyContin that is supposed to be a somehow safer alternative to the current poison pill on the market. Purdue Pharma, a criminally-convicted company, lied to the FDA, medical communities, and public before about the safety and low addiction risk of the current formulation.

The mounting toll of addiction and death as

a result of these lies and deceit is horrendous. Why should we believe that anything is different now with this new formulation? Why would we believe a criminally-convicted company whose only motivation is to continue lining their pockets with more blood money?

Thank you.

DR. KIRSCH: Before you leave the podium, could you state your name?

MS. HAYES: Paula Hayes.

DR. KIRSCH: Thank you.

The next speaker is Ed Vanicky.

MR. VANICKY: Vanicky. Happens all the time.

Good afternoon. I have no disclosures. Misbranding, illegal promotion, misleading doctors and patients, lying about the abuse potential, misleading advertising and fraud, and that’s just what they would admit to.

All of the criminal actions of Purdue Pharma resulted in billions of dollars in sales and thousands of deaths. The crimes began in meetings

such as this with the new drug application for OxyContin and with FDA approval.

Now years later and with deaths, abuse and crimes associated with OxyContin skyrocketing, they're asking you for your permission to allow them to commit these same crimes again.

Sixteen months ago, they stood before the panel and presented the usual brand of junk science and stated their claim that they had finally discovered an abuse-resistant form of OxyContin. The panel was wise enough to recognize this junk science and Purdue went home embarrassed and empty-handed.

Purdue claims to have been working on a new formulation since 2000. Other companies have created versions in as little as six months. Why has it taken Purdue so long? Given the severe problems with OxyContin, you would think the company with a conscience that supposedly puts patient safety first would have worked night and day to correct the problems with their drug or pulled it all together, for that matter.

They could have worked with other companies

that were developing abuse-resistant technology and shared ideas. Not this company, though. They would rather sue those very companies for patent infringement rather than invest the time, money, and energy in finding a solution to the problem.

So after all these years, they claim to have the correct version of it. That was not so in May of ’08 when even the company’s Vice President of Risk Management and Health Policy was quoted as saying that “We can argue that we have met some degree of tamper-resistance, but the abuse-resistance is yet to be determined.”

Are they now saying that in a scant 16 months that they have solved both of those clearing issues? The motivation here today, and it’s their only motivation, is to get this approved and begin to market it before the patent on OxyContin expires. Money drives the motivation, not a safe product for patient safety.

The national call to action to once and for all ban OxyContin and expose the real truth about this company is underway. Thousands have signed up

and thousands more will, as well. Activities are being planned around the country in an effort to educate people on the dangers of this drug.

Although it should be the responsibility of the FDA to do that, the gross lack of action by the FDA in regard to the dangers of OxyContin is forcing people to do the FDA's job themselves.

My wife Mary Jo was prescribed OxyContin for a herniated disk. A drug as powerful as OxyContin should never have been prescribed for that type of injury. Through Purdue's criminal activity, she is one of the untold numbers of legitimately-prescribed patients to die from OxyContin.

It is because of her death and all the others due to this dangerous drug that I stand before you today and remind you that although this company deceived you in 1995 when they launched the OxyContin epidemic, please do not let them deceive you today.

Thank you.

DR. KIRSCH: Thank you.

Next is Pete Jackson.

MR. JACKSON: Good afternoon. I'm Pete

Jackson. I have no financial disclosures.

The smiling girl on the screen is my daughter Emily, a friendly 18-year-old girl who died from an overdose of OxyContin in August of 2006, after she had taken one OxyContin pill offered to her by her cousin.

This was her only encounter with OxyContin. One pill swallowed whole.

What other drug can kill you like that with one pill?

I have appeared before your committees several times, as has my wife. We've begged FDA to help stem the tide of death and addiction from the non-selective widespread use of OxyContin. We are still waiting.

OxyContin is responsible for more deaths than any other drug. How many more people must die before the FDA will finally do something to stop this epidemic? I wonder how many people have died on FDA's watch since I first asked that question at one of your committee meetings two and a half years ago.

Of course, the official purpose of today's

meeting is to review once again the new drug application for OxyContin that is purportedly tamper-resistant.

Well, what about the many people like my daughter who swallowed the pill whole and then died? There are a large percentage of the total deaths from OxyContin that follow this avenue, as did my daughter. Is the new formulation somehow less risky for these individuals who swallow the pill whole? We heard this morning the answer is clearly no.

Do you even know what percentage of OxyContin victims' misuse involves tampering? Any new formulation of OxyContin will be perceived as tamper-resistant and will lead to doctors to a false sense of security, and the resulting surge in sales will lead to more deaths, not fewer. Remember, deaths track sales, period. I urge you not to endorse this NDA for OxyContin.

But today your joint committee has much more important business to conduct. FDA's mission is to promote and protect the public health. FDA has failed in this mission insofar as OxyContin is

concerned. The problem with OxyContin has existed for some time, well before this NDA. Because of this drug's continued legacy of death and addiction, Purdue's long history of unethical and illegal marketing and the company's felony record for misbranding, you must strongly recommend today that the FDA remove OxyContin from all U.S. markets.

The risk-benefit ratio of OxyContin can no longer be evaluated without considering the felony record of this company. This company should no longer be allowed to sell a drug that resulted in the deaths of thousands of Americans due to the over-prescribing that resulted from Purdue's acknowledged lies to doctors. The harm from this drug is far greater than any perceived benefits since OxyContin offers no efficacy or safety benefits over other previously-available opioid medications.

It's too late to save my daughter, but there are many other people whose lives could be saved with your voice without sacrificing access to other available opioid medications. It's time for you to stand up and do the right thing. Stop the

deaths, ban OxyContin now.

DR. KIRSCH: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration --

MS. PAUKSTIS: Excuse me. I'm Beverly Paukstis. I represent the Hospice and Palliative Nurses Association.

DR. KIRSCH: Okay. Could you --

MS. PAUKSTIS: I'll be quick.

DR. KIRSCH: No. You get your full time. Give us your name on the microphone, please.

MS. PAUKSTIS: Sure. My name is Beverly Paukstis, and I'm a member of the Board of Directors of the Hospice and Palliative Nurses Association, and I've been a nurse since 1964 and doing hospice work since 1985. I have no financial disclosure.

I represent nearly 10,000 hospice and palliative nurses who are at any given moment today

providing care to 30 to 50,000 patients in their homes who are dying, dying with pain that these nurses are seeking in partnership with physicians and pharmacists to relieve.

We in HPNA strongly and favorably support the FDA REMS process because we know that abuse and misuse occur. We are in favor of all efforts to curtail this. However, we are deeply concerned about some unintended consequences that may occur.

Specifically, we are concerned about the unintended consequences of restriction to access for the very patients that Purdue had in mind when OxyContin was developed, and that is our population of patients who are dying in severe pain.

One could argue that there are other drugs to use. The reality is, though, that we frequently see patients with allergies and patients who have such fear and anxiety over anything that mentions the word “morphine,” that they won’t take anything at all. And, as well, many of them have poor response to many of the traditionally-used opiates. It’s often necessary for us to try four or five opiates

before we find the right one.

Access to a full complement of opiates assures our ability to relieve the pain of dying patients. Eliminating OxyContin from that menu significantly harms access.

We recognize our unique role and participation with the REMS process at the time of death or discharge. We in HPNA strongly promote and vigorously teach policies for drug disposal in the home when the drug is no longer needed.

We believe it is absolutely possible to curtail inappropriate access while retaining necessary and vital access for people in pain.

Thank you.

DR. KIRSCH: Thank you. I'm going to read this again. The open public hearing portion of the meeting has now concluded and we will no longer taken comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We are now going to open the floor for questions from members of the committee to either the sponsor or FDA. Like yesterday or like usual, if you have something to say, please raise your hand. We'll write your name down here and then call you in turn.

Dr. Crawford.

DR. CRAWFORD: Thank you, Mr. Chairman. May I please ask one question to the sponsor and one to the agency?

DR. KIRSCH: Sure.

DR. CRAWFORD: Thank you. First -- well, I'll present both and whichever representative wishes to go first. One regards from the agency, Dr. P's presentation. I'm sorry. I don't want to mispronounce it.

Based on the OxyContin risk management plan and the thoughts about the class-wide risk management plan for long-acting opiates, I'm not sure what is meant with respect to the interim REMS, either for this part or in the general class-wide, what the medication guide, a little briefly, what it would entail. And you talk about a time table for

submission of assessments, because part of what I'm grappling with, with this particular product, might be any recommendations about other studies, so I need to know more about assessments.

Now for the sponsor, my question's a little different. So we've heard interesting data today from the in vitro studies and anticipated outcomes deemed likely, largely based on opinions of expert consultants and others, and very carefully-worded ways throughout this briefing document and in the presentation. And I say this in sensitivity to some of the open comments we just heard.

The words that we heard kept making sure we knew the message that you did not want to convey but it still made sure to promote in some way -- that might not be the correct word, but this reformulation suggests the reformulated tablets will be safer, the reformulation is an incremental improvement. And also we see that -- it was actually stated, the message we are trying to avoid, but to let us know that message is a new and improved formulation.

So if this product were approved, it would

be on the market, health professionals, including pharmacists, physicians, others, consumers would want to know what's going on. So I ask the sponsor exactly what is that message that would be promoted if this is on the market with a brand new formulation and lots of new questions?

DR. KIRSCH: Could I ask the sponsor to address that, please?

DR. LANDAU: Thank you for your question. It's a very important question. And before I provide a direct answer, I'll say that we're not making -- it's very clear what our motivation is to reformulate the product.

Okay. Our motivation is to address the specific vulnerability that contributes to its overall abuse liability and danger when used in various subpopulations. So we want to make that clear.

I also want to make it clear that we have no intention whatsoever of promoting the product based upon these characteristics. It's a reality that these discussions happen in an open environment.

The specific question regarding what we will say is something we have to speak very, very closely with the division and with DDMAC. We recognize we're likely to be asked these questions by pharmacists, patients are going to ask, physicians who are prescribing. And physicians might call the company through our Medical Information or Medical Services area, and we want to be certain that we don't give anyone a false sense of security that this formulation is anything it's not.

I spoke earlier to our intention to promote this product just the same way we're promoting the current product. Until post-marketing data support it, we can't assume that there's any reduction of abuse liability.

I don't know if Dr. Rappaport wants to respond to that, to the first part of the question. Sorry.

DR. RAPPAPORT: Yes, thank you. I definitely don't want to respond to the last part.

Okay. So going back, just to remind people, I think you were asking about the interim

REMS and what that is going to be.

To clarify, we're working on the class REMS for the extended-release, long-acting opioid products and we have a lot of information to go through and that's going to take us some more time. So in the meantime, we have an issue that we had to address of products that are coming up for approval that would fall into this class and what do we do with them since we don't have a REMS in place that we could implement.

What we decided, based on the fact that there are already products out there that have risk management programs that are similar to these products, such as Embeda and OxyContin in this reformulation, that it would be unfair to not approve these products with a similar risk management program, or in this case REMS for the newer products, and with an agreement in place that they would implement the new class-wide REMS as soon as it becomes available. And for the one product we approved with that, which is Embeda, the company did give us written agreement that they will implement

the new REMS as soon as we make it available.

Now the interim REMS consists of a communication plan and a med guide, and an implementation time table, but that's all. There are no elements to assure safe use. The communication plan is a Dear Healthcare Provider letter and that sort of thing, and then the medication guide is for the patients.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: Thank you. I would like to focus for a moment on the narrow question of how this formulation might represent a benefit in terms of its advance and ability to tamper with it.

I'm wondering if we could look at slide 50 for starters. That was slide 50 on the packet that we received.

DR. LANDAU: Slide 50, please.

DR. LORENZ: It shows a list of tools and it was very impressive for its length, but I guess one of the questions that impressed me is that regardless of the length of tools that do or do not work, at least 4 out of 16 do, and I wondered if

those are common tools or if in fact they were somehow difficult to obtain.

Do you think they're common tools, common household tools?

DR. LANDAU: The tools selected or evaluated of these 16 were all commonly available.

DR. LORENZ: So they're commonly-available tools.

Could we go to slide 56? So at least two of those tools produced something called particles, and on slide 56, --

DR. LANDAU: Slide 56, please.

DR. LORENZ: -- slide 56, we look at simple solvents. So I understand that the sponsor looked at the ability to manipulate the drug using common solvents, and those also are commonly available in households.

For example, at least simple solvent 6, particle size Band 6, notes that in -- that, if I understand it correctly, would show that using a simple solvent and a small particle band, which is achievable using normal household tools, right, using

a normal household solvent, that in fact the bioavailability -- well, not bioavailability, but the availability in solution of this formulation of oxycodone would be 100 percent, then, of currently-available oxycodone.

Is that a correct assumption?

DR. LANDAU: Jennifer, would you respond, please?

MS. GIORDANO: Thank you. Just to clarify how this table is set up, it's actually the amount of oxycodone that's released from the reformulated tablet divided by the amount released from the current formulation.

So what 100 represents is that the number is equivalent. However, in this situation for simple solvent 6, it's an inefficient solvent, so both numbers are low and therefore the ratio is 100.

DR. LORENZ: So using solvents that are readily available, what is in fact -- I don't know if it's correct to ask this, so you can tell me if I'm not supposed to ask it or no one needs to answer it.

But what would be -- if we were going to be

skeptics about the ability of this medication to represent an advance, what would be the largest ratio that one might achieve in common and otherwise effective solvents usually used for abuse?

MS. GIORDANO: I'm sorry. If you could clarify, I'd appreciate it.

DR. LORENZ: Solvents that are normally used by abusers trying to achieve a solution of something like oxycodone, what kinds of ratios might one expect to achieve, say, within the maximum --

MS. GIORDANO: Oh, I see.

DR. LORENZ: -- of the time frames you looked at, where not only the ratio but the amount of drug would reflect sort of common goals of an abuser?

MS. GIORDANO: We fully characterized the rate of release of oxycodone from the reformulation. I don't know how to name a number that would be considered defeat of the controlled-released mechanism. What we do know is the difference between the reformulation and the current formulation and that delta is what we set out to find.

DR. LORENZ: Okay. Well, I guess using

this slide that's present here, at least some of those comparisons would suggest that there wouldn't be a difference in terms of what an abuser might achieve, is that right? Fair to say?

MS. GIORDANO: I guess if you're speaking of numbers that are close to 100 or over 100 here -- and many of the cases, the numbers are very low and therefore the numbers are a little bit misleading.

DR. LORENZ: Okay.

MS. GIORDANO: In cases where the numbers might be high, advanced solvent number 1, these numbers, 78 and 88, those are higher numbers and more efficient extraction of the oxycodone.

DR. LORENZ: Okay.

MS. GIORDANO: But that's still a relative between one to the other.

DR. LORENZ: Okay. Well, for me, it begs a bit of a question. And I don't know that there's a good answer to this. But since we're talking about extraction rates instead of amounts, what extraction rate is clinically relevant to abuse? How much

trouble is too much trouble? Do we have any idea?

DR. LANDAU: Perhaps we can have Dr. Sellers respond to this question, please. While Dr. Sellers is coming -- oh, you have a mike. Sorry.

DR. SELLERS: The simple answer to that question is that, you know, any effort that's more than what you have to do with the existing formulation is going to have some impact. I mean, the fact of the matter is the existing formulation takes absolutely trivial maneuvers to reduce it to a powder, put it in a solution. You can snort it. You can inject it. It's a solution that isn't offensive. It isn't viscous or anything like that.

So, you know, the bar is very, very low here, and what we see in abuser behavior is that the harder it gets, the less likely it is to happen. And as I tried to indicate in my presentation, that all of these data are directional.

It is conceivable that there is some situation where the improvement will be small, but in some of these other areas, you can appreciate that the likely impact is going to be quite large on

certain behaviors by abusers.

I don't know. Does that help?

DR. LORENZ: It certainly does help. And I don't mean to be antagonistic about this, but it's an honest question in the sense that, you know, sometimes I like to make lentils. I'll put a pot of lentils on the stove with water and leave it overnight and it doesn't seem like too troublesome of a maneuver to make.

I'm not implying that that in fact is any maneuver that you might have tried here, and I'm not planning to put OxyContin in with my lentils. But it does beg the question of exactly how much trouble should be too much trouble; what kind of ratios, extraction ratios really matter.

I actually am very encouraged by the fact that you as the sponsoring company have agreed not to market on the basis of that benefit and in fact that there were epidemiologic studies on that to affirm a clinical impact on abuse. But it also for me begs the question of how this data should be interpreted and so I'm wondering what guidance you can provide

beyond the fact that indeed it is an incremental advance.

DR. LANDAU: I'll take that.

Well, that is really all we're proposing. We're learning from this reformulation and from the in vitro data that it is substantially better than the current formulation, which is so easily reduced to a fine particle size where all this oxycodone is accessed.

I'd like to return back to slide 56, if I can, to address another issue that I don't know was addressed successfully.

The 18-hour time point for these experiments is included for reference and it's part of our approach to define the failure limits of the formulation. One has to appreciate that this is a product intended for dosing every 12 hours.

So you're correct. Should one elect to lay a tablet in a glass of water for 12 hours, to be therapeutic, the oxycodone needs to be released from the formulation. So I don't know the relevance for consideration here in regard to a barrier for

manipulation the 18-hour time point confers.

One other point I'd make is that for the overwhelming majority of the time points for all of the solvents tested, the reformulated product releases oxycodone more slowly and requires more time than the current formulation.

When there are -- when release is enhanced relative to the current formulation, it's reflecting a ratio of a very small percentage difference.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: Thank you, Dr. Kirsch. I'd like to ask a question more as a point of information.

What we're talking about today is not the active ingredient but the excipient, the polyethylene oxide. And when I look up some of the prior formulations that I guess were generic but other extended-release oxycodone products that were on the market, they all had different excipients. One of them even had polyethylene glycol, which was shown that it was even on the same continuum as the polyethylene oxide.

So I guess I'm wondering why is this a new drug application since it's the same active ingredient. Forgive my -- I'm really -- I don't understand that, and forgive my lack of knowledge. But we're looking at the excipient, and it's been used a hundred other times before.

DR. KIRSCH: Will the FDA address that question, please?

DR. RAPPAPORT: Any changes to excipients with very few exceptions becomes a new drug product. There are exceptions, such as preservatives and antioxidants and things such as those, but that's not what that is in there for. The fact that it's been used in other drug products is not an issue in terms of making determination here. If the excipients were the same, it would be a generic.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: This is for the sponsor.

Did you mention anything about REMS, and will that be something that will be part of your roll-out for this product? That's the first question.

The second part of that question is will there be any training online or otherwise for prescribers for the reformulated OxyContin?

I have a couple more questions after you answer those, if you can.

DR. LANDAU: Sure. Of course. Thank you for your question.

Yes, the answer to your first question is yes, we will be rolling out a REMS. It's under active discussion with the division. We've been communicating a number of times. The composition of the REMS includes communication plan aimed at providing educational materials, both to individual prescribers based on the types of prescriptions they write and also to various and sundry medical societies that are maybe an effective vehicle for getting this type of information out to their members.

Maybe perhaps a little follow-up. In addition to the work we're doing on our product-specific REMS, we also are very much involved with 21 other sponsors, both branded and generic companies,

working very hard to create a proposal for what a class REMS should look like.

This Purdue is part of it. Of course, we're not leading it, but it is a collaborative effort and we're working with the agency and many other stakeholders to put something together as soon as we can.

MR. YESENKO: This might be for the FDA, a high-tech question that I did not get answered from the sponsor this morning regarding the ethanol dissolution. Would this be an appropriate time to ask that question?

DR. RAPPAPORT: If you're going to refer to a specific methodology using the names of the solution or that sort of thing, then it would not be appropriate. If you have a more general question, then yes.

MR. YESENKO: It's more general.

DR. RAPPAPORT: Go ahead and ask it and we'll see if --

MR. YESENKO: Yeah. It was the question that I asked this morning between the current formula

of OxyContin and the reformulated OxyContin in terms of dissolution in ethanol.

I think was it Jennifer that was going to provide that information? Was that information --

DR. LANDAU: Yes, we're happy to provide it. I'm not certain we can provide it here.

DR. RAPPAPORT: Well, if it is confidential information, that's your decision whether you want to release it.

DR. LANDAU: Sure. Will we have an opportunity to share --

MR. YESENKO: I didn't get the impression --

DR. RAPPAPORT: We could provide that information to the committee members after the meeting or if there's another break.

DR. LANDAU: Perhaps we could speak and address the question without being too specific in this forum. And with that, can we have slide 116, please?

MS. GIORDANO: Thank you. If you're speaking specifically about how the presence of

ethanol affects the rate of release of oxycodone from the formulation, this is data that was in the original NDA submission for intact tablets. And you can see on the X axis is time in minutes, on the Y axis is the amount of oxycodone released and this is a dissolution profile.

The darkest blue is the profile in SGF, light blue is 4 percent ethanol, red is 20 percent, and green is 40 percent. So as you can see, as you increase the amount of ethanol present, the rate of release of oxycodone actually slows down.

I don’t know if that helps clarify.

DR. KIRSCH: The microphone next to you is working.

Could you use that microphone, please?

MR. YESENKO: Yes, that answers my question. And then in terms of tamper-resistant properties, you mentioned that you would not be marketing that it is tamper-proof, I believe.

DR. LANDAU: No reference at all to in vitro data tamper-resistance, abuse-resistance, or abuse-deterrence. No change with respect to these

properties on a post-marketing clinical outcome without data.

DR. KIRSCH: Dr. Flick.

DR. FLICK: This question is for the sponsor. I think it's Dr. Sellers -- I apologize if I get the name wrong -- but discussed some information that's obtainable on websites, and I think this comment is to follow up Dr. Lorenz's comments about the formulation and how tamper-proof or resistant this formulation is.

I took a moment to go out to some of those websites and the quotes that I saw were somewhat different than the picture that's painted on those websites.

Within a few moments, I found out how to defeat most of these products in a very clear, concise way, written by a Ph.D. pharmacologist. I found out how to defeat the -- to extract dextromethorphan from polyethylene oxide, including pictures that described it in very clear detail.

So I make these comments only to reinforce that I don't think that any one of us expects that

this formulation or any formulation is going to raise the bar so high that no one can defeat it, but I also would emphasize, I think, that within days or weeks after the release of this product, it will be defeated and it will be defeated very relatively simply.

DR. LANDAU: Okay. I'd like to address that. I know it's not a question, but perhaps I can respond.

I would agree with your assessment of the information available on the Internet. It's actually a very valuable resource for literally real-time information on how abusers, both crude or inexperienced and sophisticated, are looking to deconstruct tablets.

We expect soon after this formulation is made available that there will be information posted on websites and that it will be part of what we track very closely to understand what's happening as a consequence.

We have reasonable expectations. This is not, as you've mentioned, a tamper-proof formulation.

We don’t at this moment have that technology available to us. What we’re looking to introduce is an incremental improvement in the robustness of the formulation to a variety of tablet manipulation scenarios.

DR. KIRSCH: Did you have another question?

DR. FLICK: I would like to just continue that question, if I could.

As a pediatric anesthesiologist, I think one of my concerns is children. And as you may or may not know, the average ingestion in children would occur in a toddler. The dose of oxycodone in a toddler is about one milligram. The doses that are being formulated here are enormous doses. For adults, they’re very large doses. For children, they are incredibly large. And I don’t -- there was a comment made that in children -- this is a safer product in children because a child wouldn’t bite it and have immediate release.

It makes no sense to me that this is at all safer for children. Children don’t typically chew these things. They would typically suck on them and

they would swallow them. So this product is no safer for children than any previous product, and I want to make sure that that's clear. And the doses here would kill a child very quickly.

DR. LANDAU: Thank you.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: Yes, my question's for the FDA and then maybe the sponsor.

Since this is a new drug application, that would mean that if a prescription was written for OxyContin substitute, you wouldn't be able to substitute. Since they're not changing the name, it's going to be a new formulation.

I mean, is that --

DR. HERTZ: The ability to substitute is solely based on the availability of generics. So that --

DR. VAIDA: But this would be a new drug.

DR. HERTZ: Right. So, for instance, a new drug doesn't necessarily have exclusivity or patent protection. It depends on the individuals. So there are new drug products that can be approved with no

ability to block a generic. So if there's a reasonable generic, then it could still occur.

DR. RAPPAPORT: There are currently no generics available and that's because of the patent that's outstanding.

DR. VAIDA: There are no generics available?

DR. RAPPAPORT: For the current formulation of OxyContin.

DR. VAIDA: For the current?

DR. RAPPAPORT: Yeah. There were for a brief while, but there are no longer.

DR. VAIDA: Okay. And then just for the sponsor, along that same line, you were saying that you're not going to advertise that this is a safer product or anything else. But as the patent becomes due, I mean are you going to -- is it going to be part of your advertisement about that other products would not be able to be substituted for this? Because the patent will be coming up, right?

DR. LANDAU: I think our expiry of patents are fairly well defined and the formulations from

generic applicants are something we're not in a position to control. So I don't know that that's a question that we could answer.

DR. VAIDA: Okay.

DR. KIRSCH: Dr. Cooper.

DR. COOPER: This is a question for the sponsor, and I certainly appreciate the expertise of the consultants and their broad experience.

However, as one of the earlier committee members noted, the wording that has been provided to us throughout the morning and the day has been regarding the likelihood of a reduction in abuse or tampering, such as likely or directional, and the data we're provided were six Internet quotations and some opinions.

I was wondering if there's any information from prior experiences, from other drugs that have been reformulated that have a high likelihood of abuse, that would provide some epidemiologic evidence that this reformulation is likely to make a difference or if there's any stronger information than these Internet quotes and opinions?

DR. LANDAU: Thank you for your question. It's a very important one.

Unfortunately, there's limited information we can draw on to understand the influence of a reformulation on patterns of abuse and shifts in abuse, methods, subpopulations. We've consulted with a number of highly-regarded epidemiologists to help us answer this question and it's part of our initiative moving forward, is to form an expert panel to answer very basic questions that are very difficult to answer.

What is the endpoint we need to be measuring? What is the study design looking forward, and how long will it take, and what type of change given an endpoint is actually meaningful in the context of a reduction in abuse?

Until we have that available, we'll continue doing what we have been doing and monitoring government source data, RADARS data and proprietary surveillance system, and monitoring the very informative Internet chat data for which we presented representative but appropriate sampling.

Dr. Sellers, perhaps you can answer.

DR. SELLERS: There is one good example and that would be Concerta. This is a controlled-release dose form of methylphenidate. It's the same kind of technology that was discussed yesterday. The Concerta version of methylphenidate was introduced by that particular company in part to address the issue of the abuse of Ritalin, which is an IR dose form. And it's quite clear epidemiologically that there is some abuse of the IR form, but when you go to abusers and you look at the epidemiology, the Concerta dose form is not abused as much and it's a substantial decrease. So that's one real-life kind of experience we have.

We have a number of others. I mean, the reference has been made or concern that, you know, some of the things we might have presented were a little selective, but, you know, when you do a search of the Internet, you create these huge long threads of information, and then you look at the patterns of abuse of what drugs show up in treatment programs and so on and so forth. And what you see is that the

things the abusers are saying they don't like turn out to map over to what is happening in practice. And Concerta is one example, but there are other examples, as well.

I gave a reference, without mentioning the drug. But there are other drugs out there that contain polyethylene oxide and abusers have views on what gelling is like.

So, you know, we don't have as much post-marketing information as is needed to precisely quantitate, but, I mean, that is a very important step that has to be done with this product and a number of others. I mean, you considered a product yesterday that the same sort of issue would come up.

DR. KIRSCH: To be explicit about the plans for this afternoon, we're running up towards the time of our scheduled break, which we're not going to have. There's a long list of people who want to ask questions and we're not going to get to the place in the agenda where we need to be by the end of the day.

So we're going to continue with the questions and not have the break at 2:15. We will at

2:30 start addressing the questions of the FDA.

So Dr. Markman.

DR. MARKMAN: John Markman. I have a question both for the sponsors as well as for the agency.

Given that this is a new drug application and that, if approved, this would replace the existing supply of medication available. And as we've heard today, there is, I think, a legacy of brand identity associated with the name OxyContin as a function of prior marketing practices and other issues, as we heard in the open session.

So what I would like to understand is if this new formulation is approved, would it be required or would the sponsor voluntarily give it a new brand identity with a new name? And the reason I ask this is I think it might have a twofold purpose.

The first is if there is going to be new messaging and new education around the properties of the drug, this would be an opportunity to begin anew with educating providers with the limitations expressed today by the sponsor.

Additionally, it might facilitate the epidemiologic studies, which are going to need to be done in order to see whether the promise of the in vitro studies is actually delivered upon when this is brought to the community.

DR. LANDAU: Can I take it?

Well, thank you for your question. As I understand it, the question is should we be considering a new identity for the reformulated product for some of the reasons you've described?

DR. MARKMAN: Yes, new drug, new name.

DR. LANDAU: Okay. Yes, so we've considered this, and our position is that we're much better off retaining the trade name for the following reasons.

The name OxyContin is recognized as one that requires, you know, substantial care in how it's prescribed and how it's handled at the patient level. We'd be afraid that changing the name of the product would not only have us lose that recognition but it might also create just what we're looking to avoid, the fact that it's a new product perhaps that's safer

with less concern required over abuse liability. We've discussed this with the agency and I think we see things the same way.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: We're asked to comment later about the overall safety profile of the drug, and in my mind the overall safety is very much driven by how it actually plays out and is commercialized in the marketplace. So I have a series of kind of related questions around that.

First of all, can you give us a bit more clarity around part of the REMS interim requirement as a communication plan, which you alluded to, which includes a Dear Healthcare Professional letter as well as a Dear Pharmacist letter?

I'm sure you've thought about the content, not just that you're sending a letter. What is the message you intend to deliver if it's not to talk about what's different about the formulation?

DR. LANDAU: Yes, I understand. Perhaps, can we have Dr. Haddox available? Thank you.

DR. HADDOX: Dave Haddox, Health Policy

with Purdue Pharma.

The message platform for both the letters going to the individuals and also to the associations that those individuals belong to is going to be re-emphasizing -- first off informing about the existence of the interim REMS, assuming that the class-wide REMS is not in effect when and if this drug is approved, because this drug will clearly be subject to the class-wide REMS once that is approved.

Part of the communication plan is to let people know that such a REMS exists, be it interim or the class-wide. So that's going to be one issue, is raising that issue.

I think that the message platform is basically going to be calling out the importance of proper patient assessment, proper management of the patients, communication with the patients about things, like safe storage, safe handling. Some of the SAMHSA data you didn't see today talks about where people who admit to non-medical use of pain relievers get their medicines, and a significant number of those get them from friends or family,

either for free, purchasing or stealing. And so the supply out there in the community is very important.

So we want to encourage pharmacists and prescribers to have those conversations with patients about this is a very important medicine; you've got to protect this and keep this for your use only. Those sorts of messages rather than saying, gee, there's something new about OxyContin. The new thing will be the REMS, either the interim REMS, if this is approved under an interim REMS, like Embeda was, or the class-wide REMS when and if that takes effect.

DR. MORRATO: So essentially generic safety messages?

DR. HADDOX: Yes, and proper assessment, proper patient assessment for both pain and also for substance use disorders.

DR. MORRATO: So if you're rolling this out to pharmacies and you're going to have a huge conversion within six to eight weeks, I think is what you were saying, they will know it's a new product number?

Will there be any sort of tracking or all

of a sudden these new tablets show up?

DR. HADDOX: Yes, they will have a new series of NDC numbers.

DR. MORRATO: Right. So they will be informed as pharmacy purchasers and distributors that something's changed, right?

DR. HADDOX: Yes.

DR. MORRATO: Okay. So what is the message then to the Dear Pharmacist? Similar?

DR. HADDOX: Yeah. We haven't really developed our -- I'm looking to our head of Sales and Marketing. We haven't really developed that. We have people that go out to the trade directly, in addition to the individual pharmacists, and we're working on that message platform right now.

DR. MORRATO: Okay.

DR. HADDOX: Part of it will be, again, to encourage and to have those conversations with people. I mean, the medication guide will clearly be part of the interim REMS, assuming this is approved on the interim REMS. So the dispenser has the obligation to hand that medication guide out.

Hopefully that's also the opportunity to have a strategic conversation with the patient or the caregiver about the content of the medication guide.

DR. LANDAU: Thank you, David.

DR. MORRATO: So I guess I would encourage the FDA, as you're negotiating the actual letter -- I mean this is really an opportunity to get those safety messages because I would anticipate, if this product is approved, it's going to come ahead of when the REMS are actually in a final form.

The other piece I would really encourage is, as I understand it at least, the FDA does not have authority as to the mailing lists that companies may choose to select to send to Dear Healthcare Professional, and that it's up to the company to provide that list. And there's variability in those lists, and I just want to make sure that it's really reaching everyone and not just a select high prescriber list.

DR. LANDAU: Certainly. I can address that. We have proposed how we would go about selecting who we send these letters to and we're

reaching very deep. Of course, those that prescribe drugs like OxyContin single-entity, long-acting opioids are very high on the list, but we'll be reaching very deep into those who prescribe short-acting opioids, as well, and have prescribed drugs like OxyContin. That's a good point.

Thank you.

DR. KIRSCH: Can I just answer, as well? We actually do have authority under the REMS policy to -- we'll work with them to make sure that it's the right group of people that are getting the letter.

DR. MORRATO: Excellent. I didn't realize that was new. Okay.

Then the other question is some have mentioned the patent expires, as I understand it, in 2013. And really, the value of the reformulation is the degree to which everyone is converted to the new formulation and stays on it as opposed to when the generic is available, they go back to it.

So regulatory, I don't have an answer, but more to raise it as a concern is thinking ahead in time in 2013, those other generics with the older

formulation will, when your current patent expires, be on the market.

So what really is the risk management plan? I know you can't control what generic manufacturers do, but I think this needs to be thought through.

So do you have any comment on that?

DR. LANDAU: That's a very interesting public health question and certainly don't have an answer to it. I think what you're getting at is if we're not marketing this product in 2013, which is not necessarily our plan, but if this was a hypothetical situation and generics were to enter the market, would they be required to have some equivalent physical-chemical properties that would otherwise be lost if this product weren't formulated?

DR. MORRATO: Right, right. So this is a new product with a new patent, right?

DR. LANDAU: Right.

DR. MORRATO: So the new NDA gives you a new exclusivity, correct?

DR. LANDAU: Well, there are patents associated with the new formulation, yes.

DR. MORRATO: Right.

DR. LANDAU: Yes, absolutely.

DR. MORRATO: Yeah. So for the FDA, when the patent expires on the current formulation, those generic manufacturers who submitted their ANDAs have the ability to go on market with the non-modified formula, correct?

DR. RAPPAPORT: That's correct.

DR. MORRATO: So we're really looking at a three-year period. Unless you're successful in showing that there's a benefit, in terms of this is really reducing abuse and misuse, which comes to my last question in terms of -- and maybe it's more of a comment -- in terms of the post-marketing studies, that I know that you mentioned are under development, the epidemiology studies, to really see how this plays out in the real world -- I'd like to see that be part of a commitment perhaps as a safety follow-up to see how this is happening as opposed to just a marketing study that gets done on the side or some transparency more as you've done with the in vitro testing, really bringing in experts in critical

evaluation of that, because it will hinge on that in the market.

DR. LANDAU: Certainly.

May I just comment on one element --

DR. KIRSCH: Please.

DR. LANDAU: -- of the previous -- one of your previous statements?

I'm the company's chief medical officer, so the patent and intellectual property considerations aren't squarely in my realm of responsibility. I'll have to check. I guess I affirmed that there are new patents associated with the reformulation. I need to check with that. That's my understanding, but I could be incorrect. So my apologies if I inadvertently misled you.

DR. KIRSCH: Ms. Solonche, you had a related short question?

DR. SOLONCHE: Yes. Thank you. Of course, we've kind of gotten off that subject now.

But my question is if and when the new versions are available, are the old versions pulled immediately or is there going to be a period of time

when both are available?

DR. LANDAU: As soon as we manufacture enough supply of the reformulated product, we will stop shipping the current product and will start shipping the new product. Within six or eight weeks or six to eight weeks roughly, 90 percent of OxyContin in the supply chain down to the retail pharmacy will be reformulated product.

DR. SOLONCHE: Thank you.

DR. KIRSCH: Dr. Day.

DR. DAY: As a member of the previous advisory committee in May ’08, I was one of the very strong critics in terms of the methods used to assess the tamper-proof abilities of the new formulation.

I would just like to comment first that this submission has taken great strides forward and is certainly much better and I was very pleased to see that.

That being said, in looking at what data are actually reported and how they’re reported, I sometimes have difficulty in answering some questions of concern.

So say for example that the table on slide 56 has come up a few times, and it's one of those tables that compares the reformulation with the original. And I do understand that that's the point of a lot of the studies, to see if there is improvement.

However, giving ratios, you know, doesn't let us assess what the absolute values are because some of us care a lot about what would be the "acceptable," if that's even a term, acceptable level of tamperability. And so there are a lot of outcome measures, whether it's amount of release or the speed of release and many, many things. And it's good we have a lot of data, but my question to the sponsor is for all the data that have been presented, either in the briefing materials before today, the handout for today and the presentation today, does the FDA and do we have all of the data both in the absolute values and in the comparison between the old and the new?

DR. LANDAU: Yes, thank you for your question. And every data point we generated through this in vitro testing program has been submitted to

FDA in our NDA resubmission.

DR. DAY: And may I ask what percentage of those have we had access to as members of the voting committee?

DR. LANDAU: I understand. I'm not sure we have the -- before I hand off to Jennifer, it was our goal to present the information. In all of the materials, the agency has asked you to consider in the most transparent and easily-digestible fashion. So if our approach is somewhat less than helpful, we'd look to the agency to make -- or perhaps we can submit additional data, raw data, if that's helpful for you to consider.

Jennifer?

DR. DAY: I was going to say the presentation is much better this time, too, and the many displays are very helpful. However, we really need an N by 2 matrix. So on the long side of the matrix is every set of type of data and then across the top is absolute values and then comparison values, and so there's not been enough time to assess what are we missing.

DR. LANDAU: I understand.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I've got three questions. One in regard to Table 56; I mean page 56. I had the same concern, that at this point where the tables are showing percent compared to the current formulation, I don't know whether seven percent is enough to kill somebody or whether a 100 percent is not enough to kill somebody. That's basically what we're asking.

So that even though the presentations are good, the fact is when Dr. Lorenz was concerned about the 100 percent, we said, oh, it's not anything to worry about, but we don't really know that for a fact.

So I think it's important to have that set of information.

The question, I think, for the FDA -- because I think you mentioned the intellectual property aspect is not the sponsor's current -- the medical director's purview-- is the issue of extending the patent with this NDA.

As I understand it, the NDA corrects a

current problem with the product. And if this correction of the issues with the product also extends the patent, I think that is information that would be helpful to have.

DR. RAPPAPORT: I think there's a little confusion between patents and exclusivity perhaps.

The sponsor will have to speak to whether they are applying for any patents, have any patents. That's not within our purview, although we can't approve generics if there are certain outstanding patents.

Exclusivity is determined by the agency based on a number of different factors. In this case, they won't be getting any exclusivity because they didn't do any clinical studies.

DR. DESHPANDE: Thank you. I appreciate that. Not being a lawyer, it's helpful to get the clarification. But it is important because this is -- I see this as a correction of existing product which you're trying to address in a good way.

I am concerned about the issue that Dr. Markman brought up, and that's the name,

OxyContin, and that coupled with the question about message to the providers with the Dear John letter that Dr. Morrato brought.

OxyContin has a certain cache in the marketplace and also on the street, and this formulation is meant to address many of the issues that brought it to the street in the first place. However, just changing it out with a new NDC number is not going to really address all of the things that you wanted it to take care of coming up with a new formulation.

So I'm a little confused about both the generic message and sort of the benefit of the name.

DR. LANDAU: Understood. Perhaps I'd like to call on a colleague of mine, Mr. Gasdia.

Would you mind?

DR. GASDIA: As was mentioned before by Dr. Landau, we considered a name change, but one of the things that we're also concerned with is that draws new attention to a replacement of an existing product that's been on the market since 1996 and has been spoken about being prescribed to millions of

patients and by hundreds of thousands of physicians. And the conversation that then starts to take place in a pharmacy becomes even more about what the differences are as opposed to a more transparent difference.

There will be a different indicia. There will be a different NDC. We do have to work on the language because we'll definitely be asked, but we want to do it in the context of what's going to be in the final package insert. We don't want to draw any extra attention. We certainly don't want to be making false claims at this point.

So we have considered it. And we've come down on the side that it actually may cause there to be more discussion about the differences by having a different brand name.

Thank you.

DR. KIRSCH: I'm going to pause for a second and Dr. Margolis has been on the telephone and want to make sure that we give him an opportunity to ask a question, if he has any.

DR. MARGOLIS: I'm fine. Thank you for

asking, though.

DR. KIRSCH: Okay. Dr. Lesar.

DR. LESAR: Based on most of my questions have been answered, so I'll pass based on time.

DR. KIRSCH: Thank you.

Dr. Lorenz.

DR. LORENZ: Thank you. I'd like to ask the sponsor what sort of -- since this is such a critical point, I'm sure there must have been some thinking about it. But what epidemiologic studies would be sufficient for the company to seek approval to market the drug as one that is abuse-resistant?

Specifically, what epidemiologic designs would you anticipate?

DR. LANDAU: That's an excellent question. The simple answer is we don't know.

DR. LORENZ: Okay. And that's a fine answer. I'd just like to make a few observations then. My concern is that many of these studies attributing causality are ecologic in nature, and I do not think an ecologic study is adequate to understand the impact of this drug for two reasons.

One is that -- well, first of all, it's a weak causal design in the first place, and I would want any design to account for trends, to account for differential efforts to improve this problem in general in society, the impact of the REMS, which could be differential from area to area for the specific drug and will be a new intervention.

Specifically looking at slide 84, there's a potential attributability to broad classes of abuse, many of which rely not only on this narrow formulation, which seems to be targeted at sophisticated users who are trying to manipulate the tablet but also to broad issues of abuse that apply to users of the entire tablet, to indeed secondary or tertiary use of the drug after it's in the community.

So my suggestion, in the absence of any others, is that causal understanding of this drug's impact on abuse will require tracing the distribution of the drug itself or the patients who are using it to understand how those drugs are then distributed and used in the community. And those are person-level designs or prescription-level designs. They're

certainly more difficult, but that's what I would think.

DR. LANDAU: Thank you for your input. I mentioned earlier we have plans to convene an expert panel of epidemiologists to have the type of discussion you just started. Thank you.

DR. KIRSCH: Dr. Zito.

DR. ZITO: I'm just reiterating several comments on surveillance at person level. Absolutely.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: I just had a follow-up to my question on new drug applications, but it was asked and answered on the patents and so forth.

DR. KIRSCH: Okay. The last question before we address the questions by the FDA will be by Dr. Flick.

DR. FLICK: In the GAO report, they outlined the sales incentives for the Purdue sales force with compensation, bonus compensation up to $250,000, as I recall.

Do you plan to change your sales incentives

or do you plan to incentivize your sales force to report misuse or misappropriation of this product?

DR. LANDAU: Yes. Thank you for your question.

Russ, could you respond, please?

DR. GASDIA: Thank you. You're correct in terms of what was found with the GAO, and we made changes several years ago, in fact going back as far as 2003, regarding the incentive plan and compensation for our sales people and have addressed those in a very dramatic way to prevent that from occurring.

We certainly don't want a system in place that encourages representatives to do things that are counter to what's in the best interests of patients and, quite frankly, in the best interests of the company because it is important that we continue to bring new products forward.

The levels of compensation are in line from our expectations in the industry. We don't see anything in our plan that over-incentivizes a rep to have the types of behaviors that would mislead. And

as we've been adding new products to our promotional efforts and we plan to add other new products in the coming years, the OxyContin percentage of their incentive plan becomes less and less.

DR. FLICK: So if I'm hearing you right, there isn't any disincentive to misappropriate and there's no incentive to report on misappropriation.

DR. GASDIA: I'm sorry. I forgot the second question. Thanks.

We actually do have a policy in place. It's been in place, I believe, since 2002, called the Abuse and Diversion Detection Program. And it's a policy that all of our representatives as well as other field-level employees of the company are trained on. And it provides them with a roadmap to try to identify behaviors or patterns that they come across during their day to day activities or they may learn of during their day to day activities. And there's, I believe, 13 different examples of criteria that they can look to to try to identify that behavior.

There's a roadmap to present that

information to our drug and pharmacovigilance group as well as our general counsel. Decisions are made as to whether we should continue to call on that physician anymore. And if the decision is made not to call on that physician or practice, the sales credit for that office is no longer calculated in any way, shape, or form for the rep.

So there actually is an incentive, and in fact the program that's been in place for seven years now encourages representatives to report any of that kind of behavior they may see or learn about in their territory.

Thank you.

DR. KIRSCH: Okay. I will end this portion of the session and go on to the questions that have been posed to the committee from the FDA.

The first is for us to discuss whether the studies performed by the sponsor adequately characterize the physical attributes of the reformulated OxyContin product. And I guess I'll start this out.

I'll re-emphasize or I'll agree with what

Dr. Day said. I was also part of the previous committee meeting and I believe that they, with this presentation, did a much better job of presenting data that was useful, at least to me, as a member of the committee.

I've just been told we need to take a five-minute break in order so the system can be reset because at the end of this, we need to have a vote and the system won't vote unless they reset it.

So we will take five minutes. Currently, it is 2:41. We'll be back here at 2:46.

(Whereupon, a recess is taken.)

DR. KIRSCH: Okay. The question that we're trying to address or that we're supposed to discuss is whether or not the studies performed by the sponsor adequately characterize the physical attributes of the reformulated OxyContin product.

My own opinion is that it does, they do, and I'd be happy to hear -- unless there's consensus. It appears that --

Mr. Denisco. I'm sorry. Mr. Yesenko.

MR. YESENKO: I'll answer for Denisco, too.

So this counts for two.

I'm just wondering why the reformulated OxyContin is changing strength, unless I'm missing something. You're adding a 15, 20, and 30. Is that -- for the sponsor, is that --

DR. GASDIA: I'm sorry. Could you please repeat it? I'm sorry.

MR. YESENKO: The question is why is the reformulated OxyContin adding a 15, 20, and 30? Is that -- I mean, does that have to do with the safety issue? Are you looking at less liability with the increments of that?

DR. GASDIA: No. I think there's a misunderstanding with that. We have seven strengths currently on the market of the current formulation. They were launched over a year and a half ago and so we have a 10, 15, 20, 30, 40, 60, and 80 milligram currently available. So we are just making the new formulation of the same strengths.

MR. YESENKO: Thank you.

DR. KIRSCH: So to summarize the opinion of the committee is that the studies that were presented

by the sponsor do adequately characterize the physical attributes of the reformulated OxyContin product.

DR. RAPPAPORT: I actually thought I heard some people in the committee who didn't fully agree with that. I just want to make sure that we've actually given everybody a chance to make their thoughts known here.

DR. KIRSCH: I think Dr. Day had some suggestions for how the data could be presented differently, but I believe that she -- I'll let her speak for herself, but didn't have recommendations for new studies, just presentation of the data differently.

DR. DAY: That is correct, but before the chair characterized everyone as being in agreement with the first question, do we want any straw vote or we'll say that we all agree, unless someone speaks up now or forever holds his or her peace?

DR. KIRSCH: The last time I tried to do a straw vote, I got hung.

DR. DAY: How about the wedding question?

We say yes, but if anyone -- you know, speak up now or forever hold your peace?

[Laughter.]

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: Well, my lawyerly question would be whether adequately implies both the clinical implications of this formulation or just simply the physical attributes, and I think I would make a distinction between those two.

DR. KIRSCH: I think the question says physical attributes.

Dr. Zito.

DR. ZITO: Yes, I had reservations based on the fact that the metrics that were used did not seem to be adequate to adequately define the issue.

DR. KIRSCH: And the issue being the clinical --

DR. ZITO: Not clinical. Based on the differences, the differences, the measurement of difference. And Dr. Day just raised the issue about whether -- so my question becomes is the existing data able to be repackaged? Is the information there

that would give us better understanding than the ratios?

DR. KIRSCH: Does the sponsor want to respond?

MS. GIORDANO: I think there's been a lot of confusion about Table 56 -- excuse me -- slide 56, the table there.

Is this what you're referring to? Could I walk you through it one more time? Would that be helpful?

I also wanted to mention that all of the data points that are represented by the ratio on that slide are in the briefing document. So I could give you specific page numbers, if that's helpful.

DR. HERTZ: Not walking us through the table again. This is Sharon Hertz. I was wondering, do you actually have the absolute data available in a slide? I think we understand that this slide doesn't provide the absolute data, and I think that's what people have been, you know, sort of hankering to see.

MS. GIORDANO: Sure. It's not put together in one particular slide, but we have numbers. We can

give you the numbers for some of the higher numbers that are represented here, if that would be helpful. And as I said, the pages, I can give you also the pages of the briefing document where the actual numbers are presented in graphical form; whatever's most helpful.

DR. DAY: Can I just comment? We're talking and focusing on slide 56 and we have an understanding of what we're looking for, but it's not just this. It's through all of the outcome measures for whenever we have ratios, do we have the absolute values and we have absolute values, do we have the ratios?

MS. GIORDANO: This slide and the following slide are the only slides that have ratios on them. I believe all the other data is expressed in either percent of release or milligram amounts in the closed session.

DR. KIRSCH: So do we have a concise way to answer the question posed by Dr. Day and Dr. Zito?

DR. LANDAU: Is this for the sponsor? I don't know that there's any concise way to provide a

response. We have thousands upon thousands of data points.

Our goal was to provide it to you in as digestible a fashion as possible. All of the information was supplied within the submission and most all of it was supplied in the briefing document. Had we looked to present all of the information, every data point, in the briefing document, it would have been unmanageable for the committee.

DR. KIRSCH: Maybe I could pose a question. Is there a combination of simple solvents and time that creates a situation where in both the new formulation as well as the old formulation there is similar and near-complete availability of the drug?

MS. GIORDANO: Not with the simple solvent.

DR. KIRSCH: And how about with the advanced solvents or pH-adjusted?

MS. GIORDANO: Your question being which ones are statistically similar in release?

DR. KIRSCH: No. Is there a combination where there is a solvent of any type that results in complete release of the drug and there’s a similar

fashion between the two formulations within 60 minutes?

MS. GIORDANO: This advanced solvent 1, the non-ingestible solvent, if you can see those numbers there, in 10 minutes with the smallest particles, you're getting 88 percent correlation between the two release rates, which is pretty similar.

DR. LANDAU: Again, these are non-ingestible solvents.

DR. KIRSCH: And at that 88 percent, is there near-complete release? It's not like the 17 or 18 percent release in both and the ratio's 88 percent? What you're saying, I believe, is that in that one that's 88, in both formulations, there's near-complete release of the drug?

MS. GIORDANO: That's right, and we can get that number for you.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: Hi. This is for Table 56. Again, I don't think it was confusing to the panel. It may have been presented in a confusing manner rather than an entire panel being confused by Table

56.

I'm wondering about the briefing document yesterday that I received in the mail. There's no way I could have reviewed that entire document. So I need to put that out on the table.

DR. KIRSCH: Thank you.

Dr. Zelterman.

DR. ZELTERMAN: I think, if I can paraphrase a comment made by Dr. Zito, when we asked her this question, are we asking that there were an adequate number of studies, should there be more studies, should there be other tests of the new formulation, or are we asking the sponsor to summarize the data better?

I think the question is a little ambiguous. You're asking studies performed by the sponsor adequately characterized. Well, what are we talking about? Is it more studies or in fact a better summary of the studies already written?

If I can go back to 56 again, this poor table, the trouble is it's very ambiguous because a 100 percent of a small number could be much smaller

than 50 percent of a much bigger number.

So when we talk about the actual numbers in this table, it's very misleading. So the 100 was said to be, well, statistically equivalent, but it's equivalent of a very small number. But just below that you see is a 58. Now that 58 might actually represent a much larger amount of drug delivered.

So the numbers themselves are not quite summarized correctly.

DR. KIRSCH: What I'd like to do is let the FDA respond to the request for clarification in the question and then I'll allow the sponsor to respond to the question.

DR. RAPPAPORT: I don't think this question is unclear. We're asking whether the sponsor has -- the studies that have been performed adequately characterize the physical attributes of the formulation. We're not asking whether they presented it well or thoroughly, but you can certainly say they haven't presented it well or thoroughly enough for us to make that determination.

DR. KIRSCH: Okay. Sponsor, do you have a

response?

DR. LANDAU: Yes. Our response is that all of the data that this slide and others are based upon are included in our resubmission, and I'd like to take a step back.

The relevant comparison -- although I recognize how important understanding precisely how much drug is released and under what condition, the relevant comparison is over the current product. And the current product, within a few seconds, is rendered in an immediate release dose form. To get to the numbers, however critical we are, represented on this page requires time, effort, tools, and determination.

So I just want to make that context clear. We're happy to provide additional clarity or transparency. It was certainly not our objective to do anything short of that. We were hoping to help the Advisory Committee and respect your time in looking to digest so much information.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I agree with you that

there’s a concern about the current product and therefore this is an effort to improve what’s on the market now.

With that, I’ll say that I am surprised that current product is still on the market with the difficulties that we’ve seen, if we’re going to address it. That’s a different issue.

For me, without the data, I can’t really answer the question about adequate number of studies because I don’t know that the data really show me the physical characteristics as I’d like to understand them.

I think Dr. Lorenz had a question about both water and alcohol and the duration of immersion or, as Dr. Flick pointed out, of having a tablet in the mouth and data from that kind of an exposure. And I wasn’t sure what the answer was there. So I’m not comfortable answering yes on this.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: I wanted to just reflect from a design of experiment standpoint in terms of the scale and scope and the different solvents, the

different extraction, the different crushing characteristics.

I thought it was a very comprehensive program which was one of the outside experts that they brought in. So from that standpoint, I think it was a very adequate set of studies to look at those attributes.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: I agree as well that it was a very comprehensive look at the tablet and there certainly is a great deal of data available.

I do question whether we've seen the data in ways that would help us easily comprehend its clinical relevance. And I also think that it's patently true that we don't really know what's clinical relevant about these ratios. And so I think the challenge would be what sort of a decision we could make on the basis of them, but that would be my concern.

DR. KIRSCH: Dr. Prough.

DR. PROUGH: It seems to me, from what we've seen, it would be awfully hard to make any kind

of case that the available data suggest that the new formulation could be more dangerous. It seems to me if there were any question about that, then the urgency of these questions would be very great.

My interpretation of the data is that the only question is the extent to which the data demonstrate that the product at least represents more of a barrier to abuse. And I think since that seems to be the fundamental question, it seems to me the studies are perfectly adequate to address that question, and the answer to that question is it's more difficult to abuse, not impossible, just more difficult.

DR. KIRSCH: The sponsor has repeatedly indicated that in the briefing material much of the information that we've been asking for is present. One of the advantages that I have of having to fly across country to get here, a lot of time in the airplane, to read the document that was sent to us the day before yesterday. And my feeling is that the information that we've been provided with does demonstrate that they've taken this question

seriously and there's always a new study that could be done. There's a lot of smart people at this table who can always think of something, another study that could be done. And we all have different preferences for how to look at data, but I think overall the sponsor, in my opinion, has done a good job of providing the data in a straightforward and complete fashion.

Dr. Flick.

DR. FLICK: I would echo those comments. I think that the data, although not well described, does answer the fundamental question. Is this more difficult than the previous formulation? I think clearly it is. Whether that will have an impact ultimately on the abuse potential and the misuse of the drug I think remains to be seen. I think the answer to the first question is yes.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: I was just going to echo that in the sense that if the second question wasn't here, I think we'd have more debate, not that I want to jump ahead. And I think even just taking out that

with the FDA, what you're really looking for, I mean, if the second question said discuss whether the studies performed by the sponsor adequately characterize the change in formulation, is that what we really want to talk about compared to the answer to the first question. But the way the first question is stated, I would have to say yes.

DR. KIRSCH: So to summarize what I hear the committee saying is that the majority, but not the entirety, of the committee believe that the studies that have been done by the sponsor do adequately characterize the physical attributes.

There is some concern about how the data was presented and it would be helpful for the sponsor to provide a more comprehensive report of the data to those who are interested. But overall the committee believes that the sponsor has adequately characterized the physical attributes of the new formulation.

Are there any edits?

[No response.]

DR. KIRSCH: We will go on to the second

question then, which I think is a much more complicated question many of the comments have skirted around, and that is to discuss whether the change in the formulation affects the overall safety profile of OxyContin.

Dr. Shatin.

DR. SHATIN: I'd like to draw people's attention to page 34. As we're talking about the overall safety profile, this looks at the recreational abusers of OxyContin. And the question is 55 percent or the mode of abuse, was through swallowing. And I think that's important to recognize in terms of the "tamper-proof" aspect of the new formulation and what that relationship might be.

I had a question related whether chewing is an additional set of patients or we could consider that as a subset of the 55 percent. So if you added those two, both would be oral and that's up to almost 100 percent.

DR. KIRSCH: Could the sponsor respond to that, please? The question relates to a particular

graph and whether or not --

DR. SHATIN: Thirty-four.

DR. KIRSCH: -- the oral and the chewed are additive or the same.

DR. LANDAU: Dr. Cone, maybe you could respond?

DR. CONE: Just so I know what I'm answering, this is the graph you're referring to?

DR. SHATIN: Yes.

DR. CONE: And could you repeat the question. I know it's about oral, but what was the specific?

DR. SHATIN: The question was the two categories of swallowing and chew, whether they're mutually exclusive or one is a subset.

DR. CONE: Yes, that's a point to be made. These are the number of responses from the people that were surveyed on the Internet. And very frequently responses were -- very frequently the person that was completing the response would indicate two or more routes of administration. And that's why the numbers don't add up to 100; they add

up to much more than 100.

So frequently they would say sometimes I swallow intact, sometimes I chew it, and even sometimes I snort it. That would be a typical response, and that's what this data shows.

DR. SHATIN: Thank you.

DR. KIRSCH: Dr. Day.

DR. DAY: On that point, was this a free response question where you would ask how do you do it, such as, or were there blanks to fill in and check or give percentage of time or say a Likert scale in terms of rating most of the time, some of the time, et cetera?

So how is the question asked, please?

DR. CONE: This is not a study I performed. This is a study performed by Nathanial Katz, and he didn't describe to that detail. He did describe the questionnaire and it was my impression that it was an open response, that you could describe how you used it and using various routes of administration. And he did have a section on validation of his response questionnaire, but that's about as far as I can go in

describing what he said.

DR. DAY: So it was open-ended, but we don't know the method of scoring. And so the question asked we can't answer as to whether the swallowers and chewers overlap.

DR. CONE: No, no, no. We can answer that question. Each one of those responses came from an individual indicating that they used by that route. The fact that some of them reported two or more routes of administration was also recorded. What I can't tell you is what the breakdown is between one route, two routes, or three routes.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: Yes. My comment is that I think we have to ask in what population maybe the change might affect the overall safety profile. And I think actually I have a fair degree of suspicion that it affects the safety profile in any user on the basis of the fact that rather simple tools and simple approaches to manipulation seem to result in the release of a large proportion of the active drug relative to the current oxycodone. And I'm not sure

that I can comment on what was illustrated in the early morning session.

But in any case, I guess the other complicating factor is whether the real issues and problems we see with OxyContin are really a function of the hard-core abusers and manipulation of the drug, and I think to that extent, the benefits would be minimal in any case. And so those are my two concerns, but my answer probably then is no, if I have to give a binary response.

DR. KIRSCH: Dr. Prough.

DR. PROUGH: I just had a question for clarification about page 34, the swallow column. Am I correct that that includes both swallowing intact pills and swallowing modified pills, dissolved pills?

DR. KIRSCH: Can the sponsor respond to that?

DR. LANDAU: Do I understand your question to be directed at more specific information within each preferred route of abuse?

DR. PROUGH: Just the one route, just swallow. Does that include intact and modified

pills?

DR. LANDAU: Dr. Cone.

DR. CONE: That is only responding as I swallowed the intact pill, no modification.

DR. KIRSCH: Dr. Crawford.

DR. CRAWFORD: Thank you. This is also very related to some of the other comments.

Dr. Cone, please don't sit down yet. Would you please go back up? Thank you.

When you were presenting, we've been talking about slide 34 and from Dr. Day's question, you placed what I inferred as you were discussing that that was the ability for the respondents to select -- in Katz's study, select more than one response. However, in your study as well as the next one on slide 35, because both of those do total 100, do we assume that it was more forced choice categories?

DR. CONE: The one on the left is an informal survey. This is not a survey that I put on the Internet and they responded to. These are the experience reports from Erowid that I went through

individually and scored each experience report as it related to OxyContin, and then I totaled up the number of responses. In that case, this is percent of responses. So it does add up to 100.

There were any number of individuals who reported more than one route of administration. So again, there was 51 respondents and 71 responses.

DR. LANDAU: Perhaps I could clarify. The last few questions on preferred routes of abuse, I think is great. We hold great interest in this for a number of reasons. And the uncertainty and the variability amongst reports are a consequence or a function of the population and the methods we're using to evaluate.

The fact is there's no national database we can use to understand the baseline for preferred routes of abuse. It just doesn't exist. So we rely on various and sundry reports, like the ones presented by Dr. Cone.

Dr. Sellers, would you mind --

DR. CRAWFORD: Actually, I don't need any more elaboration. Thank you. I just wanted to make

one more follow-up related to what Dr. Lorenz said to answer the question for the chair and the committee.

Discuss whether the change affects the overall safety profile. My opinion of that is, certainly, it is suggestive of less abuse potential, but in overall clinical use, I think we have no information that the reformulation would affect the safety.

DR. KIRSCH: Dr. Cooper.

DR. COOPER: Clearly, I think, here, I think the FDA did not present this question as a binary choice for us to say yes or no. So I think I would interpret that to mean that they want some input from us about our opinions.

Guided by the fact that the current formulation clearly has important safety drawbacks and some important design features that create risk and information about the physical properties, the opinion of experts in the field, and at least some evidence from other prior reformulations, that it seems we don’t have a burden of proof to be more likely than not or beyond convincing doubt. But my

feeling is there would at least be some incremental improvement in the safety profile.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: I thought slide 84, which was presented by Dr. Sellers, was a useful framework to think about it in terms of anticipated impact of reformulation on different population of users, experimenters, and such. And I would agree with what Dr. Cooper was saying in the sense that this is theoretical, right. So we're taking in vitro properties, and based on what we know about behaviors of abuse, we're trying to project what might happen. And so from that standpoint, it theoretically might shift the abusability risk curve. Probably more importantly, it's going to be helping regular patients who might accidentally misuse the product and safety concerns.

But I'd like to draw back to the point that, as I understand it, the current formulation, if its patent expires and you have generics in line to go to market with that same formulation that's existing, then any benefit that we have with the

reformulation is going to be fleeting in the sense that once the generic of the current formulation's on the market, it's cheaper and market forces will drive to the use of that cheaper version, which is what's now, not necessarily the reformulated one, right.

So what we're talking about might be a theoretical safety benefit and it might be short-lasting, depending on market forces.

Do I understand the patent situation?

DR. JENKINS: I think you do. It's hard for us to speculate what may happen four years hence. The standard we generally apply is you can use a withdrawn drug as the reference for approval of a generic as long as FDA hasn't determined that the drug was withdrawn for safety reasons.

So today, obviously the original formulation has not been withdrawn for safety reasons. It's still on the market. Whether four years from now, with any new accumulating data, we will consider that it was withdrawn for safety reasons is hypothetical at this point. But, in general, you can reference a withdrawn formulation

and there are many examples where the innovator has withdrawn and the generics are still there.

DR. MORRATO: So it's not certain but plausible what I'm saying could happen?

DR. JENKINS: Yes.

DR. MORRATO: Yes, thank you.

DR. KIRSCH: But I think you've heard from the committee that there's great concern over the safety of the current formulation.

Dr. Flick.

DR. FLICK: If you could put that slide back up? Thank you.

I think we've been asked to address the question does the change in formulation affect the overall safety profile. And I think when we address the various populations, I think some of those answers are more clear.

Certainly in the sophisticated addict, this new formulation presents, I think, probably little barrier to doing what they have done in the past. I think for the other populations, the formulation is less important and probably matters very little.

I think Michael Yesenko's comment about doses and the size of doses is a relevant one when we look at these populations. Very few drugs on the market in a single dose can cause death. The large doses of this drug and other sustained-release formulations of narcotics have that capacity. And one wonders whether we're focused on a formulation when we might do better to focus on the size of the dose in any individual tablet or vehicle. And I would just wonder whether the formulation is really where the focus of attention should be.

DR. KIRSCH: Thank you.

Dr. Shatin.

DR. SHATIN: The comment I had was to link pages 35 and 84. And I think, as Dr. Yesenko just mentioned, that we need to look at different categories of abusers of the drug.

As you see on page 35, there are differences in the route of administration for the recreational abuser versus abusers entering treatment. And I would think, looking at page 84, the abusers entering treatment are probably within

the sophisticated addict group. So I'm in agreement that ways will be figured out for that category. We don't know how large that group is compared to more recreational users.

Also related to your comment about the dose size, my understanding was there was a 160 that is no longer available, and maybe we should consider the 80 milligram, as well.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: This is addressing the second question discussed, whether the change in formulation affects the overall safety profile of OxyContin. Well, that's why we're here.

It's being reformulated for safety reasons because I'm assuming the first go-around, I believe it was May of '08, I was in that meeting, as well, didn't quite cut the cake. So that's why we're here back.

I have a question, though, specifically about the original OxyContin, and this might be for Dr. Rappaport in terms of the formulation of the older product and patents.

If that runs out, can that be used as a guide for a newer reformulated OxyContin?

DR. JENKINS: Let me try.

MR. YESENKO: Dr. Jenkins.

DR. JENKINS: The old formulation could conceivably remain as a reference-listed drug if we have not determined it to be withdrawn for safety reasons. That would not preclude a generic sponsor from bringing forward a formulation that has some of these new characteristics. They have to be bioequivalent. They don’t have to be exact same formulation. They have to be bioequivalent, meaning they have to have the same active ingredient, the same route of administration, the same dose, and they have to deliver the same amount to the blood, but they don’t necessarily have to have the same controlled-release mechanism. And, in fact, they often don’t have the same controlled-release mechanism.

So yes, it’s possible that generic manufacturers could bring forward formulations that have some of these physical-chemical properties that

might be desirable.

MR. YESENKO: So would that tie in to any possibility of having any further clinical hopefully appropriate studies?

DR. JENKINS: Generic drugs are not approved based on clinical studies. They're based on manufacturing. As I said, they have to be the same active ingredients, same route of administration, the same amount of drug, and then they have to be bioequivalent, meaning they deliver the same amount of drug to the bloodstream as the innovator. So there generally are not clinical studies conducted for most generic drugs.

MR. YESENKO: I guess, I'm sorry, I didn't say that correctly. I meant for the reformulated OxyContin -- this is a question, I guess, for the sponsor. Are there appropriate clinical studies that have taken place? I haven't really seen a lot of --

DR. JENKINS: They have not conducted clinical studies because they're linking the new formulation to the old formulation, based on bioequivalence, which is the same theory. They have

not been required to do new clinical trials to show that the new formulation is safe and effective because they've shown it's bioequivalent to the existing formulation.

It's the same principle that's used for approval of generics.

MR. YESENKO: But if they do, then can they get exclusivity?

DR. JENKINS: The studies have to be required for approval. So they can't just do studies in hopes of gaining exclusivity. We have to determine that the clinical studies were necessary for approval and we have not felt that they were necessary for approval. So that's why Dr. Rappaport said, you know, it's not expected that they will gain any exclusivity for this new formulation.

That's separate from patent protection, which we don't regulate. We have to honor but we don't regulate.

MR. YESENKO: Thank you.

DR. KIRSCH: Dr. Markman.

DR. MARKMAN: With respect to the intrinsic

properties of the drug, I do think this represents the possibility of an improvement in the safety profile. But I think as a field and as a society, we have a history of being wrong about what we think will be safer when it comes to opioids. So I say that with a lot of caution.

I think it's going to be critical to look at the extrinsic drug properties, you know, in clinics and in the society as a whole, and we're going to have to make a real commitment to studying this at post-marketing to really answer this question of the safety profile being improved, and I think that approval should really be contingent on a very clear plan about how we're going to demonstrate that increased safety or the lack thereof because we have a track record of being so wrong about it.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I'm still a little confused, and so when I'm thinking about the overall safety profile, particularly in comparison to the current formulation, I go back to the infamous page 56, slide 56. And for me, when I think about safety,

I think about if I take this -- if a patient takes this and that drug, is that enough to kill them or cause them harm or do something untoward, and I don't know that.

I know that in proportion to the current formulation, we have percentages of release in vitro. I don't know that a 20 kilo child or a 50 kilo adult or a 70 kilo adult will get a certain amount of medication that's enough to do him harm because I don't have the information to do it. So I'm pretty simple. I can't answer this question.

DR. KIRSCH: Dr. Zito.

DR. ZITO: I was looking at the two sheets that Dr. Shatin suggested that we look at, 35 and 84, and then the thought occurred to me that when I look at 84, I'm not seeing therapeutic misadventures in here. And then when I go back to 35, I see that abusers are what Carise, et al. is listing, and I'm not clear where misuse is.

DR. KIRSCH: Would the sponsor --

DR. ZITO: And should we not be thinking about that in terms of this second question, you

know, that the overall safety profile includes a lot of things, that bad things happen to good people aren't intended in clinical care, either because -- for all the various reasons that medical uncertainty brings.

DR. KIRSCH: Would the sponsor like to respond?

DR. LANDAU: Can we have slide 150, please? So we think this is a very important topic, patient safety, the intended patient population.

In preparation for this meeting, and it's just representative of continued pharmacovigilance, we analyzed our internal safety database, August database, and from the period from when the product was first introduced, 12 December 1995 to, in this case, 31 August, so very recent. And we queried the database for any cases involving overdose, intentional drug misuse, drug abuse, or maladministration, medication error, all cases associated with tampering, physical manipulation of the tablet. And what we found were that 1,460 cases existed and these were from multiple sources, all the

limitations of post-marketing pharmacovigilance applied.

Eighty-five percent were related to abuse, as you would expect; 15 percent were related to medication errors or maladministration.

If we can have a subsequent slide, please? Actually, go to 152.

You can see a breakdown of the 220 cases, and I won't read through this slide. The point we're trying to make here, and I think we're in agreement, is that medication errors are real; they occur. Fortunately, they don't occur with the frequency that some of the other misadventures do, but we're hoping through this slide represented, I think it was slide 34, that some of these misadventures would be avoided with the tablet that's harder to manipulate.

DR. RAPPAPORT: Can I get a clarification?

DR. ZITO: I was just going to ask for the source of the reports.

DR. LANDAU: There are multiple sources. We maintain a post-marketing pharmacovigilance database. These are reports from healthcare

providers, emergency rooms, literature, et cetera. Most of what you see -- actually all of what you see here is also included in FDA's Adverse Event Reporting System, AERS.

DR. KIRSCH: Dr. Rappaport.

DR. RAPPAPORT: So can you just clarify for me the company's opinion, and is that this new product is going to provide increased safety compared to the old product, at least for that 15 percent of patients who suffer misadventures due to incorrect use of the product?

DR. LANDAU: It's a difficult position to take, but it's intuitive to me as a practitioner. Any misadventure that involves chewing a tablet, crushing it, administration is probably less likely to occur with a tablet that's harder to crush. It's only post-marketing data would support a claim that the safety can be supported. So I don't know. I'm reluctant to make a prediction on a clinical outcome that we'd need data to support without this data.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: I just wanted to make a

comment -- this is for the agency -- that these debates are very nuanced. And I think, you know, when something makes it out to the marketplace, it's not always clear how difficult these decisions have been.

So I just want to urge the agency to maintain a public archive. And not only that, not only a public archive of the entire proceedings, but also a publicly-accessible transcript or, rather, a summary, a publicly-accessible summary of these sorts of events so that prescribers will have access to the same level of ambiguity that we find ourselves in in making such choices.

I really am saying this because, in one of the recently-approved drugs by the FDA, I became aware of the fact that there was no longer a public record of these sorts of debates. And, in fact, it was relevant to a specialty society that was putting out a notice about the availability of a new drug to prescribers. I feel it's very important to have this sort of balanced information available.

DR. RAPPAPORT: I don't know. Maybe

Kalyani wants to speak to this. But my understanding, first of all, we have our transcriber here who's getting every word

Has there been a change in the policy? We've always had complete transcripts of all of our public meetings.

MS. BHATT: Dr. Lorenz is referring to other documents. The transcripts are always available.

DR. LORENZ: Right. I'm talking to basically a web archive of the information that's informed our decisions here.

DR. RAPPAPORT: Thank you.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: I just wanted to reiterate Dr. Markman's point, maybe add a bit to it, around the importance of the post-marketing study and surveillance since we're making hypothetical leaps between what we see in vitro and what we think might happen in market.

I think that would justify the need for post-marketing studies and perhaps as part of the

risk management commitment maybe a requirement, post-marketing Phase IV requirement, in terms of this surveillance.

I know the risk management plans are supposed to be looking at diversion and abuse in general, but maybe in the launch of this drug being specific to have this drug before versus after in some of those design issues could be part of the requirement.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: Just a quick comment on that last slide and a couple of the terms that were being used.

When we're referring to errors and misadventures, the only information I've seen is on tampering of tablets. So I just want to make sure everybody understands that we're not talking about a lot of the other errors that happen out there with opioids. This is a small fraction of errors that are tampering because it was a couple other slides that said patient error or that, and it was only talking about patients chewing the tablet, not taking the

wrong strengths, not taking it in place of something else.

So even with that last slide that was shown, I just want to make sure that, from a safety profile, this is a small fraction of errors.

DR. KIRSCH: So with that, I'll try to summarize the opinion of the committee.

I think the committee has expressed great concern over the overall safety of this class of drugs, which I believe is appropriate. I think the majority believe that, although for a small subset of the patients taking these medications, this might be a safer approach. But I think the FDA and the sponsor have been loud and clear that there's enough concern about this uncertainty that the committee would like or recommends that there be a link to a required post-marketing study that will look at the clinical outcomes of this proposed new formulation.

Are there any edits to that comment?

[No response.]

DR. KIRSCH: Okay. With that, I will go on to the third point, which is our vote. And I don't

know if the FDA wants to inform us as to the mechanism of the vote.

Okay. The question is should this application for a reformulated OxyContin be approved, and ultimately we will vote yes or no or abstain. And before we have the vote, I'd open the floor for additional comments or questions.

Dr. Lorenz.

DR. LORENZ: Could you please inform us, I'm asking the agency, does a yes vote imply that this represents an advance in some sense or that it's simply safe and effective? What should we understand our vote implying?

DR. RAPPAPORT: We approve drugs based on the fact that their benefits outweigh their risks. So that would be the basis for our approval.

You don't have to consider this to be safer than the previous formulation in order to make that determination, but if that's your personal inclination, we'd like to hear that, as well. Our regulatory standard is that the benefits outweigh the risks.

DR. KIRSCH: Dr. Markman.

DR. MARKMAN: As a practitioner of pain medicine and someone who takes care of patients with chronic pain virtually every day, I first want to just attest I think to what was very powerful testimony during the open session about the efficacy of oxycodone as an analgesic or as a pain reliever. It's effective for acute pain. It's effective for chronic pain, cancer pain, and I do think there are additional benefits with regard to having a long-acting formulation of this available as a clinician. Again, I just want to attest and affirm, I think what we heard was very powerful during the open session.

I want to speak to the issue, though, of brand identity or the name of the product that I raised earlier, and again I would love to hear from my colleagues regarding this.

In my mind, the widespread adoption and success, if you will, of the use of this medication was initially associated with an unfounded claim of safety. And I think there's been a lot of unintended harm but also arguably some benefit as well, on

measure, because patients who could obtain relief from having oxycodone available have obtained it.

As a practitioner, one of the things I struggle with commonly every day in my office is that there are many patients, as a backlash to that initial unfounded claim, have a profound fear of opioids, and as a clinician I spend much of my time trying to speak to patients and compel them to try an opioid because they do have a problem from which they could benefit from this class of medication, but they're too afraid. And they're afraid because of issues of misuse, abuse, and diversion and how that's been characterized in the media, even though in their particular situation, I think that there's a very good possibility that it's their best option for relief.

That is one of the challenges of being a clinician, is trying to compel patients who are appropriate for this type of analgesic to try it. And I think that not changing the name here will continue to make that part of my job harder. And that's why I think it's important that if this is in

fact a new product and it is addressing a vulnerability of the previous formulation, that we consider not only a change in the name but again being rigorous about the new messaging around that new name and new product.

DR. KIRSCH: Dr. Cooper.

DR. COOPER: So the agency has told us that sort of the standard to think about for this question is deciding whether the benefits outweigh the risks for this particular decision, and I think that when I think about that, I'm thinking about the old formulation versus the new formulation. And for me, I think that, given the risks the old formulation has, even recognizing the concerns that some folks have addressed, the clear echo and the clear need for post-marketing studies, I think that I feel comfortable saying that the benefits for this new formulation would outweigh the risks, if that's the standard we're applying.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: Well, we've been all over the map today on many different issues, but it comes down

to the one thing that's changed is the excipient. And we're being asked to approve this reformulated OxyContin, and since the only thing that's been changed is the excipient, I can only say is that change better?

The old drug will still be here, whether this is changed or not. So the only thing I can do is say is the new formulation better than the old? We're not voting on the class of drugs or whether to approve OxyContin. I do think there are some implications with the name, and again that points to my confusion.

It's a new drug application. There are excipients that, according to the pharmacopeia, in the previous generics that were delayed formulation release excipients. So this issue gets confusing. If it's a new drug, it gets a new name.

So this whole issue still goes around a little bit. I know it's covered by laws and regulations, and sometimes they'll chase their tails and some of that we've done, you know, ourselves. So I'm just going to make it very simple for myself and

base it on what has changed and is that change favorable to the public health or unfavorable to the public health. And I'd also like to echo that all the public comments were very, very informative and much appreciated.

DR. KIRSCH: Dr. Flick.

DR. FLICK: Two comments. First, I would also like to acknowledge the public comments, and in particular the comment of the father whose child took a single dose of this medication and died.

I think that I've made this point before and I'll try and make it again. I think one of the risks that is inherent in this drug and the drug that we considered yesterday is not the vehicle, it's the dose. The doses that are available in a single tablet here are very, very large doses, that most of us around the table could not take one of these upper-end doses. And it seems to me that if we're interested in making this a safer product, then we would consider reducing the maximum single dose. I will leave that for the consideration.

My next comment is I'm not sure that we're

actually being asked to approve or disapprove of this particular formulation, although in actuality I suppose we are. We have an alternative. The alternative is we approve this new formulation or we leave the old one on the market. That's really the question.

Clearly, this formulation is somewhat, although I would say very incrementally, safer than the previous formulation, it does represent a small advance.

DR. KIRSCH: Dr. Lesar.

DR. LESAR: Just a couple comments. My thought process is I believe this is a better dosage form. If it was 1995 and this drug was just first being marketed, it would clearly be a safer product. However, what we've learned in the past number of years in the use of this drug is that the history has sort of changed the way we should think about this. So I believe it's safer; it could be safer in a subset of patients.

I believe one of the ways it could have been presented clearer was what is the dose that

people inject, so that on that table on page 56, what was the number, how much does it take for me to get 10 milligrams in five ccs of saline? So if I had an 80 milligram tablet, how easy is it to get a dose that I want, either orally or by injection? So I thought that could have been improved.

I think trying to determine what the net effect on public health is very difficult to say. And I think this drug is a safer dosage form. However, the net effect will depend on how it's used and used in people who do not disrupt the dosage form, and I think that will have to do with what the unintended consequences. And I just wanted to read a headline about us today in what's called *MedPage Today.* It's a news item and it says, "FDA Panel to Review Tamper-Resistant Oxycodone."

My hope is that if we do approve this product or do vote for approval, that it does not say tomorrow the FDA panel votes to approve safer OxyContin.

DR. KIRSCH: That's pretty dramatic.

Dr. Margolis has again been quiet. I want

to give him the opportunity to ask any questions or make a comment, if he has one.

DR. MARGOLIS: Yes. Thank you. It's sort of been difficult to participate in this way, but I agree with the comments that are being made.

I mean, it does appear that this will be a somewhat safer product, but it's very difficult to really know how much safer it's really going to be. As an epidemiologist, you know, our guesses are really theoretical in terms of which groups it's going to be safer in. It's certainly not going to be safer in those who are taking a large dose accidentally or any that are due to medication errors.

I think post-marketing's going to be incredibly important here, and just how much safer it's going to be for the vast majority of the people who are using it will be difficult to know.

DR. KIRSCH: Thank you.

Mr. Yesenko.

MR. YESENKO: I'd like to echo Dr. Flick's comment about the fact that if we do vote yes on this

reformulated OxyContin, are we then saying or are we then asking the sponsor to pull the old formula or the old dosage of OxyContin?

DR. KIRSCH: That's what they've agreed to.

MR. YESENKO: Okay. And then the second comment is the open session with the families and friends of those who have died from OxyContin, my heart goes out to you. And my fear is if we do accept or do vote to approve a reformulated OxyContin, my fear is that in two years, will there be public comments in this open forum with some of us on the panel with family members who have died from taking the reformulated OxyContin.

Thank you.

DR. KIRSCH: I answered for the sponsor. I hope they agree. The question was if this current formulation is approved, I heard you say over and over again that within six or eight weeks you would have 90 percent of the pharmacies and so forth retooled with this new formulation and would ultimately take the old formulation off the market.

DR. LANDAU: That's correct.

DR. KIRSCH: Thank you.

Dr. Tortella.

DR. TORTELLA: Thanks. I think from the industry standpoint, the data really show three activities identified to abuse, and that's chew, snort, and shoot. Hardening in the gel formation after hydration I really think move us forward in addressing those big three areas.

Thank you.

DR. KIRSCH: Thank you. Dr. Lorenz.

DR. LORENZ: Actually, what was I going to say? I'll think about it.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: I think this product probably isn't safer and I think we echoed a lot of those comments in that, but we are just voting on the reformulation. So I know the FDA wanted to know if we thought it was a safer product. I'd have to say I don't think it's a safer product, but the reformulation may have less abuse potential.

Just to answer Dr. Markman, I appreciate what you're saying about with the name changes, but I

think actually what you came out with is my real concern with the name change, is that this is still oxycodone. It's still an opioid, and even as you brought it out, that you may come across the patients as a safer product and as a product that maybe isn't an opioid.

So I'd have real concerns about actually even recommending a name change at this time.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I think this is a very difficult vote and before we take a formal vote, I appreciate the chance to comment.

First of all, the families that spoke, both in favor of long-acting opiates and those who talked about the family tragedies, are exactly the two ends of my practice, the pediatric critical care and pediatric anesthesia and pain management.

So I'm having some real conflicts here because I think the drugs are important. As Dr. Markman and others have pointed out, it's an important part of our armamentarium. So what I've not heard -- and this is where I think as an advisory

panel to the FDA, we need to give this advice, not just to vote yes or no on this but collectively the advice, as Dr. Lorenz talked about keeping a record of it.

First of all, looking at Dr. Katz's paper in *Clinical Journal of Pain*, swallowing was 55 percent of the abuse or the misuse. Swallowing is a significant concern for both young and adolescent and old patients and how that plays into the problems associated with these medications is something we haven't looked at.

The second is that we have talked about an immediate REMS, but we really haven't talked about a REMS for this product, and one of the things that I am struggling with is that, yes, I would like to have a potent opiate to use for the cancer pain patients and others who have long-term chronic pain.

I also want to make sure that there's a safety plan in place that's more than a Dear Doctor letter. And we've heard that it's in the works, but my advice is that we need a REMS to go along with this, and I'd like that in the record as a sense of

the committee.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: Jut a narrow comment about the issue of dose, and I just want to comment as a hospice and palliative medicine physician that the higher doses are extremely helpful. In fact, we use extremely high doses of opioids in many patients that would alarm, I'm sure, a lot of people at this table. And it's just a problem, I think, to deal at such dose levels sometimes with multiple tablets.

So I'm not saying one way or the other about whether it should be done because I think this is an issue of balancing public risk and benefit. I don't mean to suggest that therefore enormous doses should be available. It's just that it points out the effect to which the eventual impact of this drug on public health depends on the market that the sponsor seeks. And I think one of the concerns that we all have at this table is that the FDA be highly vigilant about ensuring that the market is narrow and appropriate and that it doesn't cause increased public risk through misperception of benefit. And so

I think I personally have no concerns, again like Dr. Prough noted before, that this is any less safe than what we have to deal with and may be incrementally better.

But if it displaces many other opioids or patients with stable pain regimens, then who really knows, and I think then the social consequences are likely to be different.

DR. KIRSCH: Dr. Zito.

DR. ZITO: Well, I concur with many of the points that have just been made, and one has to do with the narrowness of the population of patients that are being targeted. So I think the marketing is going to be extremely critical.

Secondly, the point that Dr. Markman raised about an opportunity could be missed here without taking advantage of a change in the name, because it's a busy world out there and folks are just going to proceed with business as usual, I think. So while we get maybe a narrow benefit here for this targeted abuse population, it's everyone else that we really have a chance to weigh in on now.

DR. KIRSCH: Dr. Crawford.

DR. CRAWFORD: Thank you. Just very briefly, as we're looking at this question as to whether we recommend approval of the reformulated OxyContin, we are all keeping in mind the limited scope with which this committee has been charged to answer, which essentially is current formulation or reformulation. And if time allows, since we might be close to a vote now, perhaps the agency or the chair would entertain suggestions about under which conditions, because it's a yes/no vote, but perhaps the members of the committee might recommend certain conditions that FDA could consider if they were to approve the drug.

DR. KIRSCH: I think that the FDA would appreciate your opinion about what conditions you believe are important, but I don't see that as part of the vote. But if you have further comments to make about what conditions you think are important, I'm sure the FDA would appreciate those comments.

DR. CRAWFORD: Well, thank you. One has been stated several times before without specificity,

and I won't add any more to that, except I think it's extraordinarily important that a condition of approval for consideration would be mandated study, clinical follow-up studies on the -- it seems a clear therapeutic benefit in general; we already know that, but about the safety of a reformulated product.

DR. RAPPAPORT: Can I make a comment? It's very unclear to everybody, all the stakeholders here, what the right study is to do and how long you have to do that study to collect the information in the community, and even if it's ever going to be possible.

So I'm not saying we don't agree with you that a study should be done, but for us to mandate or require a study, we have to know what that study is so that we can tell the sponsor at the time of approval. So if anybody here feels very strongly about what that study should be, I hope you'll say so.

There are a number of groups that are looking at this right now and trying to come up with at least a proposed protocol for this type of study,

but I think that's a ways off.

DR. KIRSCH: Dr. Zelterman.

Dr. Flick.

DR. FLICK: Just a response to Dr. Lorenz. , I think that there's -- as a practitioner of pain, as well, I recognize the need for large-dose increments in a really select few patients that we deal with but aren't really part of most of the patients that these drugs have been used by and this drug continues to be used by.

I think there's a psychological barrier for the casual user or the occasional user, the person that I have great concern about, that Dr. Deshpande voiced concern about, that there's a psychological barrier to taking one, two, three, four of these tablets as opposed to taking a single tablet.

Very few of the uninitiated would believe that taking a single tablet of a prescription medicine is potentially a fatal dose. So that's my comment about the dose size.

I think the problems with OxyContin have come primarily less about its formulation and more

about its marketing and more about the way it has been marketed by the company that is the sponsor. We have very little reassurance and very little information brought to us today that would inform the committee that there is substantial change and that there is an expectation that this will not happen in the future.

I know the company has made changes, has been forced to make changes, but I don't know that we have a clear, as Dr. Deshpande pointed out, a clear REMS that we can look at and approve and comment on. So in the absence of those things, I find it difficult to answer in the affirmative the question whether this should be approved.

The conundrum once again is that we are forced into a position of saying we either stick with the old or go with the new. And clearly the old is worse than the new, although I think the difference is relatively small.

DR. KIRSCH: Dr. Shatin.

DR. SHATIN: Yes. I'd like to address a benefit in patient safety that I think we should

explicitly recognize and that's the misuse of the tablet form for both caregivers, and then thinking about institutions and facilities, that if it's not chewable that is a benefit.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: I had a question of clarification. When we vote, is that when we're supposed to provide our justification or rationale; are we supposed to provide it now?

DR. KIRSCH: Perfect segue, I think, into what will happen. For those of you who haven't voted on this committee, in the very near future we'll be given instructions. This thing in front of us will light up and you can press yes or no or abstain, and then we'll complete our voting. But before we display our votes on the screen, we'll ask Dr. Margolis to vote, not knowing what the rest of us have voted, and then his vote will be entered into the system, and then the screen will show all of our votes. And then we'll go around and ask again for comments as to why we voted the way that we did.

Did I explain that correctly?

[Dr. Rappaport nods yes.]

DR. KIRSCH: Okay. So with that, I'm going to try to summarize what I believe we've said in this section.

First and foremost, several people have said, and I'll reiterate, that we all have great concerns for the families who either have members who suffer great pain or who have suffered great loss because of inadvertent use of this drug. I think the committee really feels for both sides and this is a very difficult question.

I think the committee overall believes that the new formulation is not necessarily safer but that there is less chance of poor outcomes related to drug manipulation or tampering with the tablet.

I think where there's great concern and will probably shift people from saying yes to no or no to yes relates to the REMS. I think there's great concern expressed by many people on the committee that the REMS is not well defined, and for a drug with this level of danger, the REMS is very important. And so I think that's a concern expressed

by most of the members of the committee.

Are there desire to edit my comments?

Dr. Lorenz.

DR. LORENZ: It's unclear to me that this drug's benefits are certain or quantifiable. They are hypothetical on the basis of limited physical manipulations under accidental circumstances.

DR. KIRSCH: Thank you.

So with that, I'll ask that we take the vote. Does someone from the FDA want to make our things light up or they're lighting up? Okay.

So from the members of the committee, again you press the yes or no or abstain button and we'll be given further instructions.

Yes, you do it right now.

It will keep blinking until they finalize the vote and they'll watch it on the computer to see whether or not all of us have voted, and when all of us have voted, they'll let us know and then we'll get Dr. Margolis's vote.

I'll reread the question. Should this application for a reformulated OxyContin be approved?

Yes or no or abstain. Everyone please vote again.

Okay. Dr. Margolis, can you tell us what your vote is?

DR. MARGOLIS: You want just my vote or vote and reason?

DR. KIRSCH: No, just give us your vote for right now.

DR. MARGOLIS: My vote is yes.

DR. KIRSCH: Okay. So the vote was yes.

Now we can display the votes.

[Votes displayed]

Okay. So these are the summary votes, and I assume here in a second you're going to display the individual votes and what I'd like to do is read the results.

So the voting results are yes-14, no-4, and abstain-1.

What I'd like to do is go around the table and briefly have people explain why they voted as they did, and it's perfectly acceptable to say that I have nothing to add for why you voted.

So let's start with Dr. Prough.

DR. PROUGH: Since it was basically a question of the risk-benefit ratio of the new formulation, the new formulation appeared to add no risk and possibly offered some benefit.

DR. KIRSCH: Dr. Zito.

DR. ZITO: I found it difficult to vote yes without conditions, namely improved oversight of benefit, study of benefit, and then around the issue of whether the educational program with given the same name is really going to be effective.

DR. KIRSCH: Dr. Cooper.

DR. COOPER: I concur with Dr. Prough.

DR. KIRSCH: Dr. Crawford.

DR. CRAWFORD: I voted yes because everything I saw, I agree with what the sponsor's conclusions were, that the reformulation was "not more susceptible to manipulation, not worse than." And it does appear from the in vitro studies compared to the existing formulation that there is lesser potential, at least now, for abuse.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I voted yes with regret,

and it was on the narrow question of whether this was not worse than the current formulation. It adds a minor benefit. I would like to add strongly that the FDA take into account all of the advice and the concerns expressed by the committee here today.

DR. KIRSCH: Dr. Markman.

DR. MARKMAN: I voted yes for the reasons stated by Dr. Cooper and Dr. Prough. I also feel strongly that the risk management plan as well as the post-marketing studies will be critical to really understanding whether this is a safety advance.

DR. KIRSCH: Dr. Day.

DR. DAY: I abstained because I think there are strong needs of patients for this drug and proper use in prescribing, yet there's incredible risk in other situations, and it got deadlocked for me. And if it had been binary and I was forced to choose, I probably could have narrowed the question more to just is it no worse than the original, and I would have voted yes.

DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: I voted yes on the basis of

the fact that it appears to be no worse. My concern, however, is that it could be much worse, especially if marketing allows providers to drop the vigilance that they typically use in prescribing opioids. And so while I voted yes, it only assumes the status quo. Should that change in any way, it could be a definite no.

DR. KIRSCH: Dr. Margolis.

DR. MARGOLIS: I voted yes for the previously-stated reasons, that it has potential to be safer. However, how much safer is really unknown, and it's going to be very dependent on good post-marketing studies.

DR. KIRSCH: This is Dr. Kirsch, and I voted no because I felt that, although the data was much better than it was at the previous presentation, I think it's unconscionable to move forward without a well-defined REMS.

Dr. Lesar.

Sorry. Dr. Zelterman.

DR. ZELTERMAN: I voted yes for reasons already given.

DR. KIRSCH: Ms. Solonche.

DR. SOLONCHE: I voted yes for many of the reasons cited and for the particular way in which this question was asked.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: I voted yes for the reasons given and on the principle of balance. It seemed all things balance, that this was some small incremental improvement. However, I must say I'm terrified over, one, unintended consequences, and two, over the report we heard on the Internet and how this is going to be reported and publicized. And it really won't matter what the REMS is if we hear tomorrow on the news that all of a sudden OxyContin is safer.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: I voted yes for many of the reasons already mentioned, and I just wanted to add my concern, also, in terms of what gets actually communicated as opposed to an implied claim versus what you actually claim on a label. The message gets out there nonetheless.

I think when given the choice between

leaving what's existing on the market with doing nothing, at least when you have the window of launch, you have a chance to have some action. And I'm really concerned that the class REMS are going to take far too long to really make a difference.

DR. KIRSCH: Dr. Lesar.

DR. LESAR: I voted yes for the reasons already stated and have the same reservations that have already been expressed.

DR. KIRSCH: Dr. Shatin.

DR. SHATIN: I voted yes for the reasons already given, and I also strongly believe that the post-marketing and REMS will be extremely important.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: Yes. I voted yes for the reasons given and that hopefully it's not worse than what's on the market.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: I voted no because I'm horrified of the fact that there is no REMS available and the lack of clinical safety presented by the sponsor.

DR. KIRSCH: Dr. Flick.

DR. FLICK: I voted no. I think the company sponsor has done a good job of presenting their product. They did good work. I think they came here in good faith. And I think the new formulation does, indeed, do what they set out to achieve.

Unfortunately, by approving this drug, we lose leverage. We no longer can demand -- or at least our ability to demand is less than it was before. We can't have them come back with a REMS or ask them to reduce the dose availability.

So I think for that reason, I reluctantly voted no, recognizing that the old formulation would have remained on the market.

DR. KIRSCH: I'd like to thank the public speakers. I'd like to thank the sponsor for their excellent presentation, and I'd like to specifically thank Kalyani Bhatt for pulling this all together for us. I think we're done.

Thank you.

DR. RAPPAPORT: I'd like to add the FDA's

thanks to the committee members for helping us out. This is a really difficult one, as you found out yourselves today.

Thank you.

[Whereupon, the meeting was adjourned at 4:13 p.m.]